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## Progress Toward Transforming the Integrated Risk Information System (IRIS) Program: A 2018 Evaluation

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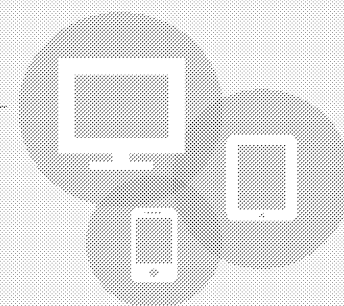
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# **Progress Toward Transforming the Integrated Risk Information System (IRIS) Program: A 2018 Evaluation**

Committee to Review Advances Made to the IRIS Process

Board on Environmental Studies and Toxicology

Division on Earth and Life Studies

**A Consensus Study Report of  
*The National Academies of*  
SCIENCES • ENGINEERING • MEDICINE**

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This Consensus Study Report was reviewed in draft form by persons chosen for their diverse perspectives and technical expertise. The purpose of this independent review is to provide candid and critical comments that will assist the National Academies of Sciences, Engineering, and Medicine in making each published report as sound as possible and to ensure that it meets institutional standards of quality, objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process.

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Lisa Bero, University of Sydney  
Nancy Reid, University of Toronto

Although the reviewers listed above provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations of this report, nor did they see the final draft before its release. The review of the report was overseen by Mark Cullen, Stanford University, who was responsible for making certain that an independent examination of the report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content rests entirely with the authoring committee and the National Academies.

The committee gratefully acknowledges the staff of the US Environmental Protection Agency, especially Tina Bahadori and Kristina Thayer, for their presentations to the committee during open sessions. The committee is also grateful for the assistance of Norman Grossblatt who served as the report editor.



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## Summary

Over the past several years, the US Environmental Protection Agency (EPA) has been transforming the procedures of its Integrated Risk Information System (IRIS), a program that produces hazard and dose–response assessments of environmental chemicals and derives toxicity values that can be used to estimate risks posed by exposures to them. The transformation was initiated after suggestions for program reforms were provided in a 2011 report from the National Academies of Sciences, Engineering, and Medicine that reviewed a draft IRIS assessment of formaldehyde. In 2014, the National Academies released a report that reviewed the IRIS program and evaluated the changes implemented in it since the 2011 report. Although it provided many recommendations, the 2014 report concluded that “substantial improvements in the IRIS process have been made, and it is clear that EPA has embraced and is acting on the [National Academies] recommendations.”

Since 2014, new leadership of EPA’s National Center for Environmental Assessment (NCEA) and IRIS program has instituted even more substantive changes in the IRIS program in response to the recommendations in the 2014 report. Given the new direction of the IRIS program, EPA asked the National Academies to review the agency’s progress toward addressing the past recommendations. Accordingly, the National Academies convened the Committee to Review Advances Made to the IRIS Process. The present committee heard presentations, reviewed posters, and received demonstrations of toolkits and databases from EPA over the course of a 1.5-day workshop, and it reviewed recent IRIS work products. This brief report provides the committee’s general findings regarding EPA’s progress (Chapter 2) and specific findings regarding changes made in response to individual recommendations from the 2014 report (Appendix E).

Overall, the committee was impressed with the changes being instituted in the IRIS program since the 2014 report. The committee views the transformation of the IRIS program as a work in progress, recognizes that this review assesses one moment in time in a still-evolving program, and acknowledges that the IRIS program will (and should) continue to evolve as it adapts and applies new scientific approaches and knowledge. The change in NCEA and IRIS leadership has led to substantive reforms, and there is strong evidence that systematic review methods are being developed and implemented and that there is a commitment to use systematic-review methods to conduct IRIS assessments. Although the committee offers some refinements and identifies a few possibilities for further development in Chapter 2, its overall conclusion is that EPA has been responsive and has made substantial progress in implementing National Academies recommendations.

## 1

## Introduction

For many years, the National Academies of Sciences, Engineering, and Medicine has been asked to review assessments produced by the Integrated Risk Information System (IRIS) of the US Environmental Protection Agency (EPA). The reviews have consistently provided recommendations for revisions of specific assessments, but the National Academies committee that was tasked with reviewing the draft IRIS assessment of formaldehyde also suggested changes to improve the IRIS program itself, if EPA chose to do so. Since release of that committee's report (NRC 2011), the IRIS program has been undergoing substantive changes. In 2014, another National Academies committee reviewed the changes in the IRIS program and provided an overall favorable assessment, noting that it was reviewing a work in progress (NRC 2014). In light of a change in leadership and continued revisions of the IRIS program, EPA asked the National Academies to review changes since 2014 and to determine whether they have been responsive to the recommendations in past National Academies reports. In response to EPA's request, the National Academies convened the Committee to Review Advances Made to the IRIS Process, which prepared this brief report.

### THE INTEGRATED RISK INFORMATION SYSTEM AND PREVIOUS NATIONAL ACADEMIES REPORTS

Given problems in several IRIS assessments noted by previous National Academies committees (see, for example, NRC 2006, 2010, 2011) and specific issues encountered in the formaldehyde assessment, the committee that evaluated the formaldehyde assessment provided a roadmap for reframing the development of IRIS assessments (Chapter 7, NRC 2011). The roadmap did not provide detailed guidance but rather suggestions for creating a more systematic and transparent IRIS process, if EPA chose to go forward with reforming the process. Congress directed EPA to respond to and incorporate the recommendations and suggestions provided in Chapter 7 of the 2011 National Academies report (House Report 112-151; Public Law 112-74). EPA indicated that the agency was committed to responding to National Academies recommendations and improving the IRIS program and began to make substantive changes. In a 2012 report to Congress, EPA highlighted its intended changes, such as a new document structure with a preamble that describes general methods for evidence identification, evidence evaluation, and derivation of toxicity values; new systematic approaches for data analysis; and expanded efforts for stakeholder engagement (EPA 2012; NRC 2014). EPA also noted that it had formed the Chemical Assessment Advisory Committee under the auspices of its Scientific Advisory Board to advise the agency on specific assessments and broader program issues. To ensure that EPA was responding adequately to National Academies recommendations, Congress asked the National Academies to review the changes that EPA was implementing.

In 2014, the National Academies released the report *Review of EPA's Integrated Risk Information System (IRIS) Process* (NRC 2014), which evaluated the changes that were being implemented in the IRIS program and assessed whether they were responsive to the recommendations and suggestions made in Chapter 7 of the 2011 report. The 2014 report concluded that "substantial improvements in the IRIS process have been made, and it is clear that EPA has embraced and is acting on the recommendations in the...formaldehyde report." It urged EPA to adopt systematic review practices, framed the IRIS process

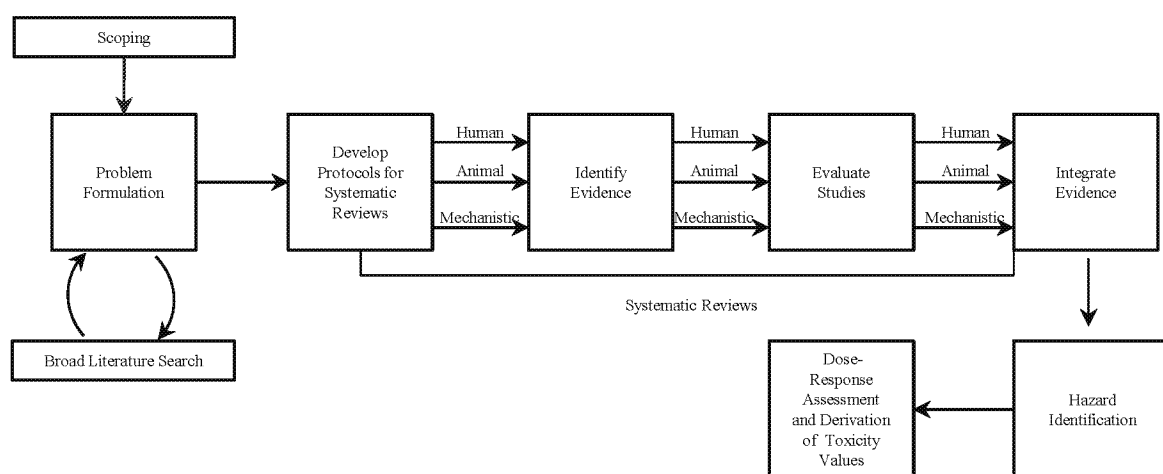
## Introduction

in the context of systematic review (see Figure 1-1), and provided specific recommendations on each step of the process (NRC 2014). Since release of the 2014 report, substantive efforts have been made to incorporate systematic review into the IRIS process, and EPA has now asked the National Academies to assess its progress.

### THE COMMITTEE, ITS TASK, AND ITS APPROACH

The committee that was convened to address EPA's request included expertise in toxicology, epidemiology, risk assessment, statistics, modeling, evidence integration, and systematic review; see Appendix A for biographic information on the committee. The verbatim statement of the committee's task is provided in Box 1-1. As noted, the committee was asked to assess the changes that have been (or that are planned to be) implemented by EPA in response to National Academies recommendations. It is important to note that the committee was not asked to evaluate the overall value of the IRIS program, to recommend where IRIS should be located within the agency, or to review any specific chemical assessment. The committee was also not tasked with conducting a comprehensive review of the IRIS program; rather, it was asked to evaluate whether the current trajectory of the program agrees with past recommendations of the National Academies.

To address its task, the committee held a 1.5-day workshop during which EPA presented its progress to the committee. Multiple opportunities for stakeholder input were provided. Appendix B provides the workshop agenda. The committee reviewed EPA presentations (Appendix C), posters (Appendix D), recently released materials (EPA 2017, 2018a,b; Orme-Zavaleta 2018 ), and all materials submitted by stakeholders. To fulfill its task of evaluating EPA's progress in implementing past National Academies recommendations, the committee decided to focus its attention primarily on recommendations made in the report *Review of EPA's Integrated Risk Information System (IRIS) Process* (NRC 2014). Although the report *Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde* (NRC 2011) provided general suggestions for reforming the IRIS program, it primarily made recommendations specifically for revising the draft assessment of formaldehyde. It is important to note that the 2011 committee was not tasked with an extensive review of the IRIS program. The 2014 report considered the general suggestions provided in the 2011 report, reviewed the IRIS program specifically, and made numerous recommendations directed at the program. Therefore, the present committee considered the 2014 report as expanding on the suggestions provided in the 2011 report and thus evaluated EPA's progress in addressing each recommendation in the 2014 report.



**FIGURE 1-1** The IRIS process in the context of systematic review. Source: NRC (2014).

*Progress Toward Transforming the Integrated Risk Information System Program: A 2018 Evaluation***BOX 1-1 Statement of Task**

An ad hoc committee under the auspices of the National Academies of Sciences, Engineering, and Medicine will assess changes that have been implemented or plan to be implemented by the U.S. Environmental Protection Agency (EPA) for its Integrated Risk Information System (IRIS) in response to recommendations made in previous NRC reports, such as *Review of EPA's Integrated Risk Information System (IRIS) Process* and *Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde*. The committee will base its assessment on EPA presentations and interactive sessions during a 1.5 day workshop at which multiple opportunities will be provided for stakeholder input.

**ORGANIZATION OF THE REPORT**

The present report is organized into two chapters and five appendixes. Chapter 2 presents the committee's overall findings regarding advances made in the IRIS process. Appendix A provides biographic information on the committee. Appendixes B, C, and D provide the workshop agenda, EPA presentations made during the workshop, and EPA poster presentations, respectively. Appendix E details the committee's findings concerning individual recommendations in the report *Review of EPA's Integrated Risk Information System (IRIS) Process* (NRC 2014).

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## 2

## Responses to National Academies Recommendations

Over the course of a 1.5-day workshop, the US Environmental Protection Agency (EPA) made presentations to the committee on changes that are transforming the Integrated Risk Information System (IRIS) process. The committee used that information and recently released IRIS documents to judge the extent to which EPA has adequately addressed recommendations made in previous National Academies reports, primarily *Review of EPA's Integrated Risk Information System (IRIS) Process* (NRC 2014).<sup>1</sup> The committee's overall comments are provided below; findings regarding individual recommendations are in Appendix E.

### GENERAL PROCESS ISSUES

The 2014 report (Chapter 2 in NRC 2014) offered recommendations related to the IRIS process and evaluated EPA's progress in implementing the suggestions made in *Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde* (NRC 2011).<sup>2</sup> Above all, the 2014 report commented on the need to continue to sustain the evolution of the program's procedures and to consider how EPA will do so in the context of continually advancing scientific methods. In the 4 years since the 2014 recommendations, the IRIS program clearly has maintained a trajectory of change that has accelerated under the new leadership of the EPA National Center for Environmental Assessment (NCEA) and the IRIS program. The committee was impressed by the scope of changes that have been or are being implemented and by the engagement of scientists throughout NCEA, EPA more broadly, other federal agencies, and academe to effect change. Such engagement is appropriate inasmuch as funding for the use of external contractors has diminished, and there is expertise in relevant fields throughout the agency. Supervisory and communication strategies are in place, and formal quality management has been implemented. The committee notes that EPA will need to ensure that quality management extends to activities that are conducted by people who are outside the IRIS program.

Changes in some of the critical elements of the overall IRIS process are still in progress. The 2014 committee was given an incomplete draft of the handbook; the handbook is intended to provide guidance on the IRIS process. The 2014 committee recommended completion of that handbook; the present committee was not given a draft of the handbook. EPA indicated that the handbook is still in development and is "being updated to reflect Agency input, evolving IRIS practices as systematic-review approaches are tested through implementation, and public comment received on chemical-specific protocols" (Slide 22, Appendix C). Public release is anticipated in 2018. The handbook is expected to provide critical guidance for the development of IRIS assessments, and the present committee urges that high priority be given to its completion, peer review, and release. Reference to it will facilitate transparency on the approach for specific IRIS assessments. In the absence of a final version of the handbook, EPA is describing its approach for the reviews in its protocol documents, and this practice provides transparency into the assessment process while the handbook is being completed. The committee notes, however, that the handbook should not become a final, fixed set of guidelines but rather should be a document that evolves over time.

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<sup>1</sup>Referred to hereafter as the 2014 report. The committee that produced that report is referred to as the 2014 committee.

<sup>2</sup>Referred to hereafter as the 2011 report.

## Progress Toward Transforming the Integrated Risk Information System Program: A 2018 Evaluation

The 2014 committee also commented on the need to incorporate input from various stakeholders—including industry, academe, and nongovernment organizations—at appropriate points in the process; this recommendation has been heeded by past and current program leaders. Three points in the process, including development of assessment plans and systematic-review protocols, have been identified at which public comments will be sought (slide 24, Appendix C). Although the present committee was not shown the approach for acknowledging public comments and incorporating them into the process, the handbook should describe how this will be done. The committee was impressed by other NCEA program activities that engage stakeholders, including dissemination of tools that it has developed, such as the benchmark-dose (BMD) modeling software, and provision of training.

EPA also commented that it was moving away from a one-size-fits-all approach to what it termed a *portfolio approach*, as described in Box 2-1. The move toward a portfolio approach appears to add need-based and context-based flexibility to the IRIS program. EPA used chloroform as an example; it is developing a reference concentration for inhalation exposures and assessing whether the reference concentration protects against carcinogenic effects adequately. The decision to limit the assessment was based on consultation with EPA regulatory programs. Overall, the portfolio approach is expected to conserve agency resources, and it is consistent with the recommendations of the National Academies report, *Science and Decisions: Advancing Risk Assessment* (NRC 2009).

### SYSTEMATIC REVIEW: PROBLEM FORMULATION, PROTOCOL DEVELOPMENT, AND EVIDENCE IDENTIFICATION AND EVALUATION

The 2014 report offered many recommendations related to systematic review, including problem formulation, protocol development, evidence identification, and evidence evaluation (Chapters 3–5, NRC 2014). The committee found that the IRIS program has made substantial progress in incorporating systematic-review methods into its process and assessments. Development and implementation of systematic-review methods have been facilitated by the recruitment of the current IRIS program director, who has extensive experience in the development of the methods and their application to chemical risk assessment. The IRIS program has also expanded internal training programs that are designed to improve staff understanding of the methods.

#### BOX 2-1 Environmental Protection Agency Description of Its Portfolio Approach

To ensure...support is timely and responsive, NCEA is developing a portfolio of chemical evaluation products employing the principles and state-of-the-art practices of systematic review. The portfolio approach will increase public health protection by:

- moving away from a “one-size-fits-all” approach to chemical risk assessment towards a spectrum of assessment products to meet specific decision contexts;
- facilitating the incorporation of new science into risk assessment and decision-making;
- tailoring assessments to meet the many needs of decision makers; and,
- increasing the number of chemicals that can be evaluated for their effects on human health by utilizing constrained resources in the most efficient manner.

Source: EPA (2018a).

*Responses to National Academies Recommendations*

Furthermore, the IRIS program has developed a number of formal and informal collaborations with groups that are active in systematic review, including the National Toxicology Program Office of Health Assessment and Translation, the World Health Organization (WHO), the European Food Safety Authority, the International Collaboration for Automation of Systematic Reviews, and the Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies (CAMARADES). Some of those collaborations help to position the IRIS program as a leader in advancing systematic-review methods, such as the development or modification of risk-of-bias tools for animal toxicity studies.

The committee was impressed by the efforts of IRIS program management to develop within the IRIS program the scientific expertise needed to conduct systematic reviews. Some notable changes have included the establishment of a systematic-review working group that should lead to increased efficiency and consistency among assessments. Other workgroups that are focused, for example, on epidemiology, physiologically based pharmacokinetic (PBPK) models, and neurotoxicology have been created; these teams of appropriate subject-matter experts are expected to support the IRIS process further through improved rigor of scoping and problem formulation and through improvements in other steps of the systematic-review process.

The 2014 report offered numerous recommendations related to systematic-review processes that are accepted as standards of practice in the scientific community. The present committee found multiple examples of the IRIS program's consideration and implementation of those recommendations, such as the development of systematic-review protocols, inclusion of an information specialist who is trained in systematic-review methods in the work groups, and the use of two-person teams for data extraction and risk-of-bias assessments. The IRIS program is also appropriately using a variety of software tools to assist with literature management (HERO), scoping (SWIFT), screening (Distiller), and data extraction (HAWC). The use of those and other software tools with input from appropriate subject-matter experts should improve efficiency, transparency, and rigor and directly address recommendations in the 2014 report. Many of the operational approaches used by the IRIS program are described in the assessment plans or the systematic-review protocols, and sufficient details are given to provide assurances that standardized systematic-review methods are being developed and applied by the IRIS program. The committee expects future systematic-review protocols to be streamlined and to become less generic when the handbook is completed.

The 2014 report also offered several recommendations about evaluating individual studies. Those recommendations encouraged EPA to use or develop tools for assessing risk of bias in different types of studies (human, animal, and mechanistic) and to add quality-assessment items relevant to particular systematic-review questions. EPA has implemented a process for evaluating risk of bias, and several documents that were provided to the committee (for example, EPA 2018b; Orem-Zavaleta 2018) demonstrate implementation of EPA's risk-of-bias tools and how EPA has augmented them with additional question-specific elements to assess study validity. The IRIS program, however, should provide information on the choice and use of tools, including its rationale for the choice of particular risk-of-bias domains. Including that documentation in the IRIS handbook will improve transparency. The committee notes that evaluation of risk of bias, although important, is not the only way to evaluate study quality. Accordingly, the IRIS program should show how other important methodologic characteristics of a particular study will be evaluated, and EPA should continue to seek and evaluate additional tools that can help to assess study quality.

As part of revisions of the IRIS process, EPA is producing assessment plans and systematic-review protocols. The committee found overlap between those documents; for example, PECO statements are found in both types of documents.<sup>3</sup> Indeed, the added value of a two-step process (assessment plan and protocol) was unclear to the committee. It was not immediately clear whether the assessment plan also serves as a "data call" for additional studies that are outside the scope specified by the systematic review but could inform the overall chemical-assessment process. Some additional clarification of terminology and clearer descriptions of how the documents will be used could help the public to understand how chemical assessments move through the IRIS process.

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<sup>3</sup>A PECO statement is a structured framework that defines a question by specifying population, exposure, comparator, and outcome to be considered in a systematic review.

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The committee identified several ways in which the IRIS program could benefit from refinements. For example, the link between scoping and problem formulation outlined in the assessment plan and development of the PECO statement was not well described. Improving the description of how scoping and problem formulation are used to focus the goals of a systematic review will lead to greater specificity in descriptions of outcomes, inclusion and exclusion criteria, and other elements found in the systematic-review protocol and will further improve the transparency and scientific rigor of the process. The committee found that the IRIS program included the dates and results of its literature searching and screening (for example, as appendixes) in draft systematic-review protocols that are undergoing public comment. Completing the literature search as part of protocol development is inconsistent with current best practices for systematic review, and the IRIS program is encouraged to complete the public-comment process and finalize the protocol before initiating the systematic review. Doing so will improve transparency in the IRIS process.

The committee identified several recommendations in the 2014 report that reflect broad scientific efforts that extend beyond the IRIS program. For example, several recommendations were related to the evaluation and use of mechanistic data in a systematic review. EPA's systematic-review process indicates that mechanistic data can be considered at various steps; for example, the draft protocol for the IRIS assessment of chloroform (EPA 2018b) describes how mechanistic data will be considered. Although appropriate tools, such as those to evaluate risk of bias in mechanistic studies, are in early stages of development in the broader scientific community, the IRIS program has developed approaches for the evaluation of PBPK models that will be used in assessments (Orme-Zavaleta 2018). The committee expects similar evaluation methods for other types of mechanistic evidence to emerge on a case-by-case basis and to include methods for determining at what stage and how mechanistic data could be used in an IRIS assessment. For example, mechanistic data were used by a National Academies committee to inform development of PECO statements for reproductive outcomes associated with *o*-phthalate compounds (NASEM 2017a). The committee notes that the use of mechanistic data by the IRIS program is consistent with other EPA programs, such as the Office of Pesticide Programs; for example, in the recent hazard identification conducted for benzo[a]pyrene (EPA 2017b), the IRIS program used mechanistic data extensively. Nonetheless, establishment of a framework for when and how mechanistic data would be identified, evaluated, and used remains challenging. The challenge is not unique to the IRIS program and has been identified for future work in the National Toxicology Program (NTP) handbook for conducting systematic reviews and evidence integration (NTP 2015a, p. 73–74).

Finally, the committee considered best practices for systematic reviews in other medical disciplines. Current best practices recommended by the Institute of Medicine (IOM 2011) suggest that the IRIS teams involved in the systematic-review process should be independent of those involved in regulatory decision-making who use the products of the systematic-review teams. The committee notes that the current organizational structure of the IRIS program in the EPA Office of Research and Development is consistent with those best practices.

## EVIDENCE INTEGRATION

The 2011 report recommended standardizing an approach for synthesizing evidence within data streams (human, animal, and mechanistic) and integrating evidence across data streams (NRC 2011, p. 165).<sup>4</sup> From 2011 to 2013, the IRIS program moved solidly in that direction, as evidenced by its draft handbook (EPA 2013) and its example applications of the approach in two draft IRIS reports—the Toxicological Review of Methanol (Noncancer) and the Toxicological Review of Benzo[a]pyrene (see NRC 2014, pp. 93–96). Although the 2014 committee recognized that substantial progress had occurred during 2011–2013, it made several additional recommendations to guide the IRIS program toward a more systematic

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<sup>4</sup>IRIS uses the phrase *evidence synthesis* to refer to the task of combining evidence from a given evidence stream, such as human or animal, and the phrase *evidence integration* to refer to the task of combining evidence from different evidence streams.

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process for evidence synthesis and integration that would maximize transparency, efficiency, and scientific validity.

The major recommendation in Chapter 6 of the 2014 report guided IRIS to choose between making its current guided expert process more transparent and adopting a more structured, GRADE-like,<sup>5</sup> process along the lines of the NTP (NRC 2014, p. 105). The IRIS program has explicitly chosen the first option, using structured categories with criteria to guide expert judgment, and EPA has made substantial strides toward more systematic and transparent evidence synthesis (see slides 65–84, Appendix C; posters D-4 and D-5, Appendix D). Specifically, the IRIS program has created processes and guidelines for synthesizing human evidence and animal evidence that support choosing one category for characterizing the strength of evidence (see slides 82–84, Appendix C). The guidelines focus on human and animal evidence streams and use mechanistic evidence to inform evidence synthesis and to provide scientific guidance for evidence integration in the steps that follow. In using Bradford Hill criteria to move beyond association to causation and to build on the systematic evaluations of individual study quality conducted in the step before evidence synthesis,<sup>6</sup> the IRIS program has created a process for evidence synthesis that is scientifically consistent with the state of the art and that effectively leverages approaches of other programs, such as NTP, that face similar challenges. Increased transparency is evident in the examples and the workshop presentations, but further transparency would be obtained with completion of a handbook that provides more details about processes, reasoning behind decisions, and approaches for presenting results. In the interim, while EPA is completing its handbook, it is releasing protocols for each assessment that include a description of how evidence within each data stream will be synthesized and how evidence from multiple data streams will be integrated. The draft protocol for the IRIS assessment of chloroform (EPA 2018b) was provided as an example. The committee supports EPA's approach.

Integration of evidence across data streams was described by EPA in its presentations (see slides 79–87, Appendix C; posters D-4 and D-5, Appendix D) and in the draft chloroform protocol (EPA 2018b, pp. 43–53). Again, the process and framework within which evidence integration takes place (slides 82–84; Appendix C) are consistent with state-of-the-art approaches taken by other scientific institutions or agencies, such as NTP, that face similar challenges.

Some questions have been raised about the use of mechanistic data in evidence integration. When animal or human data are extensive, mechanistic data can be used to evaluate the evidence within or across the animal or human data streams rather than as a third stream of evidence to be analyzed separately and then combined with human and animal evidence. When extensive mechanistic data are available and human and animal data on apical end points are sparse, mechanistic data might be used reliably as a third data stream to identify hazards, as has been done for the dioxin-like polychlorinated biphenyls (IARC 2016). Mechanistic data are important in identifying potential adverse outcomes, including ones that are not evaluated in guideline-driven animal testing; in informing dose–response assessment; and in determining the relevance of animal data for human health risk estimation. For example, in the case of phthalates (poster D-7, Appendix D), mechanistic data were used to determine that not all effects on male reproductive development in rodents were relevant for humans, and the data provided a basis for selecting the studies that were most relevant as a starting point in establishing a reference dose. However, EPA acknowledged that understanding of mechanisms relevant to effects of phthalates on development is incomplete, and that uncertainty makes it difficult to estimate risk primarily on the basis of mechanistic information. Although organizing the body of evidence according to a mechanistic framework might at first seem desirable because of biologic relevance, mechanistic frameworks today could probably be completed for only a few chemicals. As noted in the 2014 report, solid conclusions about causality can be drawn without mechanistic information,<sup>7</sup> for example, when there is strong and consistent evidence from animal or epidemiology studies.

<sup>5</sup>GRADE is defined as grading of recommendations, assessment, development and evaluation.

<sup>6</sup>For example, see slide 69 in Appendix C, in which EPA advises using only medium-quality and high-quality studies and incorporating considerations of bias and sensitivity.

<sup>7</sup>“The history of science is replete with solid causal conclusions in advance of solid mechanistic understanding” (NRC 2014, p.90).

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Another recommendation from Chapter 6 of the 2014 report concerns expanding EPA's capacity to perform quantitative evidence integration for hazard identification, for example, by using meta-regression or Bayesian analysis. To avoid compromising efficiency and timeliness in producing assessments, the 2014 report recommended developing such analytic capacities in parallel with other work in the IRIS program. EPA has taken the recommendation seriously and has explored meta-analytic approaches to combining animal data within species to determine whether the evidence indicates a chemical hazard, for example, whether trimethylbenzene poses a neurotoxic hazard (poster D-2, Appendix D). The IRIS program also initiated work on a Bayesian approach to combining data from different animal species (poster D-10, Appendix D).<sup>8</sup> The Bayesian work is promising, but application to IRIS assessments has not yet occurred. It is clear that the IRIS program has made progress here; the agency should continue with its efforts in this field.

Another recommendation from both the 2011 and the 2014 reports urged the use of more standardized, structured evidence tables to support the evidence-integration narrative<sup>9</sup> and emphasized the utility of a somewhat standard template for the narrative. The 2017 Toxicological Profile for Benzo[a]pyrene (EPA 2017b) provides an example of structured evidence tables that directly support the evidence-integration narrative, first for synthesis of individual data streams and then in an integrated summary form that connects evidential categorization with the supporting studies (Table 1-20, page 1-108). The final table lays out the evidence that the chemical is a human carcinogen by first introducing the human evidence on cancer from benzo[a]pyrene or precursors from complex mixtures and the human mechanistic studies and then discussing the findings of in vivo animal studies on tumors associated with multiple routes of exposure, adding the studies of precursor events, and finally presenting the evidence that precursor events are likely to occur in humans. The format is clear, well structured, and straightforward to follow. Although a well-reasoned discussion on noncancer effects is available in the same document, structured-narrative justifications of the evidence-integration process and the conclusion were not as well developed as those on cancer. In the workshop, EPA stated that standardized descriptors for noncancer effects are still needed and are being discussed within the agency.

EPA illustrated current thinking regarding the template for evidence integration in the workshop (slide 85, Appendix C) and in the chloroform draft protocol (EPA 2018b). The template has many characteristics of the GRADE approach to evaluating evidence, with similar labels for conclusions about the strength of the evidence within and across data streams. The approach appears to conform with the state of the art and bears considerable similarity to the system used by NTP (NTP 2015a,b). Although the chloroform protocol provides some illustration of EPA's approach, more detailed guidance and completed examples are needed to judge EPA's application of the template for evidence integration.

In summary, the IRIS program has made substantial strides in meeting the recommendations of the 2011 and 2014 reports regarding synthesis and integration of evidence. The IRIS process that was presented to the committee is dramatically more systematic, transparent, and scientifically defensible than the one presented in the 2010 IRIS Toxicological Review of Formaldehyde (EPA 2010).

## DERIVATION OF TOXICITY VALUES

Recommendations regarding derivation of toxicity values were provided in Chapter 7 of the 2014 report. An important recommendation in that chapter was to "develop criteria for determining when evidence is sufficient to derive toxicity values." In the workshop, EPA described the overall process and criteria that the agency intends to use to implement that recommendation and indicated that it would develop toxicity values when the evidence-integration conclusion is the "strongest" or a "moderately strong conclusion for a human health effect." As noted, EPA clarified that the agency intends to systematize processes

<sup>8</sup>The Bayesian approach is based on the seminal work of Dumouchel and Harris (1983) and recent work of Jones et. al. (2009).

<sup>9</sup>An evidence-integration narrative is a description of the available evidence and the argument for or against a particular hazard.

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to maintain transparency in reaching the hazard conclusion (slides 132–133, Appendix C), although standard descriptors for noncancer effects are being reviewed within the agency and are not yet final.

EPA's approach is consistent with the 2014 recommendation that formal dose–response assessments should be restricted to outcomes on which evidence integration has led to the strongest or a moderately strong conclusion on the given health effect, such as known or likely to be carcinogenic to humans (slide 131, Appendix C). EPA indicated that when there is less strong evidence on a human health effect, such as suggestive evidence of cancer, the decision to develop a toxicity value will be determined by the situation (for example, when there is a well-conducted study and a value would be useful for a decision). However, EPA did not present criteria to be used in such cases.

The one example in which criteria have been applied to support the derivation of toxicity values was the chloroprene reassessment (Orme-Zavaleta 2018). In that document, EPA focused its systematic review on publications since the 2010 assessment. EPA concluded that the new studies did not change the conclusions in the 2010 assessment and did not justify a reassessment of human health effects (that is, derivation of new toxicity values). Although commenting on the conclusions in that assessment is beyond the scope of the present committee's task, the committee acknowledges that EPA's reassessment described its criteria for evaluating risk of bias and study sensitivity needed to detect a true effect and that it presented criteria for evaluating PK/PBPK studies. Furthermore, EPA explained why each study considered in the final assessment did not change the conclusions reached in the 2010 IRIS assessment and did not justify a reassessment of human health effects. Thus, it is clear that EPA is making progress toward improving transparency in its use of systematic review and expert judgment to inform the derivation of toxicity values directly.

Another important recommendation in the 2014 report was that EPA “continue its shift toward the use of multiple studies rather than single studies for dose–response assessment” (NRC 2014). The present committee noted that progress has been made in the use of multiple studies for dose–response assessments as exemplified in the recent assessments of ethylene oxide and benzo[a]pyrene (slides 134–135, Appendix C) and builds on efforts to compare candidate reference doses or concentrations in previous assessments, such as in the 2012 IRIS Toxicological Review of Tetrachloroethylene (EPA 2012). EPA is further developing new tools for visualizing comparisons to communicate the outcome of assessments more effectively, as was demonstrated in the workshop by using HAWC. EPA acknowledged, and the committee agrees, that the development of systematic assessments for many types of mechanistic studies that could contribute to the assessment remains challenging, not only to EPA but to the scientific community generally. However, the process that EPA previously developed to review PK/PBPK models and to describe how they could be used in dose–response and toxicity-value assessments (EPA 2006) is a good example of best practices. As other forms of mechanistic data become more readily available, partly driven by previous National Academies reports (NASEM 2017b; NRC 2007), the IRIS program should develop new approaches for using such studies to inform dose–response and toxicity-value assessments (slides 142–147, Appendix C). Such guidance will improve transparency and encourage new science, whether it is used to support evidence of potential toxicity or, just as important, to provide perspectives on the potential exposure conditions that could reasonably be expected to cause toxicity.

The 2014 report also recommended that EPA use formal methods for combining multiple studies and further develop and expand its use of Bayesian and other formal quantitative methods for dose–response assessment and derivation of toxicity values (NRC 2014). EPA has begun to develop and apply tools for meta-regression analysis and Bayesian approaches and has demonstrated their application in case studies (slides 135, 136, 139, and 140, Appendix C; posters D-2 and D-10, Appendix D). Implementation of the recommendation will continue and will require sustained resources and continued capacity-building to develop a process that is ultimately transparent, is replicable, and represents best practices for the future. And it will require close collaborations between domain experts in the biologic and mathematical or statistical disciplines within EPA and with other agencies and stakeholders to establish clear criteria and guidance, including articulation of underlying assumptions, strengths, and weaknesses of each approach. The committee notes that care must be taken when combining results within or between studies in developing dose–response relationships inasmuch as multiple mechanisms, each with its own potential dose–response relationship, might be involved. In such cases, clearly articulated expert judgment, criteria for expert selection,

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and multidisciplinary collaborations need to be supported and used in the development and application of new mathematical approaches.

The 2014 report recommended that EPA develop IRIS-specific guidelines to frame analysis and communication of uncertainty (NRC 2014). EPA has made substantial progress in developing and adopting tools to address uncertainty analysis and communication (slides 136–138, Appendix C; poster D-6, Appendix D). It demonstrated its work during the workshop and focused on model uncertainty (slide 136, Appendix C) and the probabilistic distribution of toxicity values (slides 137–138, Appendix C). It further indicated that the IRIS program intends to adopt the WHO/International Programme on Chemical Safety guidance (slide 137, Appendix C) and to provide various calculations when reporting toxicity values, including ranges of risk-specific toxicity values (slide 138, Appendix C) to demonstrate uncertainty. The committee recognizes that the steps taken are in the right direction for an evolving process and encourages EPA to continue to develop and test new tools in collaboration with other agencies and stakeholders. Equally important, the committee encourages EPA to continue its effort to frame uncertainty analysis and communications to address multiple sources of uncertainty surrounding toxicity values.

### CONCLUDING REMARKS

Overall, the committee is encouraged by the steps that EPA has taken, which have accelerated during the last year under new leadership. During the workshop, the committee was impressed by the overall enthusiasm displayed by EPA staff and the substantive progress toward full implementation of systematic review and transparency in IRIS assessments. The committee fully appreciates that changing the process and implementing systematic-review procedures while producing final assessments is a huge challenge for any organization, especially in such a short period (12 months) and with a shrinking staff. Because new tools and approaches will ultimately be needed to implement past National Academies recommendations, especially for incorporating mechanistic information and for integrating evidence across studies, the committee is encouraged by IRIS program efforts to collaborate with other EPA staff, other government agencies, and academe to have the right mix of expertise to develop new approaches and best practices for conducting assessments.

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## Appendix A

### Biographic Information on the Committee to Review Advances Made to the IRIS Process

**Jonathan M. Samet** (*Chair*) is a pulmonary physician and epidemiologist. He is the dean of the Colorado School of Public Health and previously served as a professor and Flora L. Thornton Chair of the Department of Preventive Medicine of the Keck School of Medicine of the University of Southern California (USC) and director of the USC Institute for Global Health. His research has focused on the health risks posed by inhaled pollutants. He has served on numerous committees concerned with public health: the US Environmental Protection Agency Science Advisory Board; committees of the National Academies, including chairing the Biological Effects of Ionizing Radiation VI Committee, the Committee on Research Priorities for Airborne Particulate Matter, the Committee to Review EPA's Draft IRIS Assessment of Formaldehyde, the Committee to Review the IRIS Process, and the Board on Environmental Studies and Toxicology; and the National Cancer Advisory Board. He is a member of the National Academy of Medicine. Dr. Samet received his MD from the University of Rochester School of Medicine and Dentistry.

**Richard A. Corley** (retired) was a laboratory fellow at the Pacific Northwest National Laboratory operated by Battelle for the US Department of Energy. Dr. Corley specializes in the development of physiologically based pharmacokinetic models, real-time breath analysis, dermal and inhalation bioavailability, and the development of three-dimensional computational fluid-dynamic models of the respiratory system. He has published numerous peer-reviewed papers on oral, dermal, and inhalation toxicology; on modes of action of a variety of industrial and consumer chemicals; and on pharmacokinetic modeling and its applications in human health risk assessment. Dr. Corley has served on several National Academies committees, including the Committee to Assess the Health Implications of Perchlorate Ingestion, the Standing Committee on Risk Analysis Issues and Reviews, the Committee to Review EPA's Draft IRIS Assessment of Formaldehyde, and the Committee to Review EPA's Draft State of the Science Paper on Non-monotonic Dose Response. He received a PhD in environmental toxicology from the University of Illinois at Urbana-Champaign.

**George Daston** is the Victor Mills Society Research Fellow at the Procter & Gamble Company. He has published over 100 articles and book chapters and edited five books in toxicology and risk assessment. His current research efforts are in toxicogenomics and mechanistic toxicology, particularly addressing how findings in these fields can improve risk assessment of chemicals and the development of nonanimal alternatives. Dr. Daston has served as president of the Teratology Society, as councilor and treasurer-elect of the Society of Toxicology, and on the US Environmental Protection Agency Science Advisory Board, the Board of Scientific Counselors of the National Toxicology Program, the National Academies Board on Environmental Studies and Toxicology, and the National Children's Study Advisory Committee. He is editor-in-chief of *Birth Defects Research: Developmental and Reproductive Toxicology*. With scientists at the US Humane Society, Dr. Daston manages the AltTox Web site, which is devoted to the exchange of scientific information leading to the development of in vitro replacements for toxicity assessments. Dr. Daston has been awarded the Josef Warkany Lectureship and the Distinguished Service Award by the Teratology Society, the George H. Scott Award by the Toxicology Forum, and the Society of Toxicology's Best Paper of the Year Award, and he is an elected fellow of the American Association for the Ad-

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vancement of Science. Dr. Daston is an adjunct professor of pediatrics at the University of Cincinnati. He earned his PhD in developmental biology from the University of Miami.

**David Dorman** is a professor of toxicology in the Department of Molecular Biomedical Sciences at North Carolina State University. His research interests include neurotoxicology, nasal toxicology, pharmacokinetics, and cognition and olfaction in animals. He has served on advisory boards for the US Navy, the National Aeronautics and Space Administration, the US Department of Agriculture, and the National Toxicology Program. He has chaired several National Academies committees, including the Committee on Endocrine-Related Low Dose Toxicity, the Committee on Predictive-Toxicology Approaches for Military Assessments of Acute Exposures, and the Committee on Design and Evaluation of Safer Chemical Substitutions. He was also a member of the Committee to Review EPA's Draft IRIS Assessment of Formaldehyde and the Committee to Review the IRIS Process. Dr. Dorman is an elected fellow of the Academy of Toxicological Sciences, is a fellow of the American Association for the Advancement of Science, and is a national associate of the National Academies of Sciences, Engineering, and Medicine. He received a DVM from Colorado State University and completed a combined PhD and veterinary toxicology residency program at the University of Illinois at Urbana-Champaign. Dr. Dorman is a diplomate of the American Board of Veterinary Toxicology and the American Board of Toxicology.

**Russ Hauser** is the chair of the Department of Environmental Health, Frederick Lee Hisaw Professor of Reproductive Physiology, and professor of environmental and occupational epidemiology at the Harvard T.H. Chan School of Public Health. He also holds an appointment at the Harvard Medical School, where he is professor of obstetrics, gynecology, and reproductive biology. Dr. Hauser's research focuses on the effects of environmental chemicals on reproductive health, pregnancy, and children's health. He has served on several National Academies committees, including the Committee to Review EPA's State of the Science Paper on Nonmonotonic Dose Response, the Committee on the Health Risks of Phthalates, and the Committee on Endocrine-Related Low-Dose Toxicity. Dr. Hauser was a member of two US Environmental Protection Agency Science Advisory Boards, served on the US Consumer Product Safety Commission's Chronic Hazard Advisory Panel that examined the effects of phthalates on children's health, and is an associate editor of *Environmental Health Perspectives*. He received his MD from the Albert Einstein College of Medicine and his MPH and ScD from the Harvard T.H. Chan School of Public Health, where he also completed a residency in occupational medicine. He is board-certified in occupational medicine.

**Karen A. Robinson** is an associate professor at the Johns Hopkins University School of Medicine. She also serves as director of the Johns Hopkins University Evidence-Based Practice Center and is a member of the core faculty in the Center for Clinical Trials and Evidence Synthesis at the university's Bloomberg School of Public Health. Her research focuses on evidence-based health care and evidence-based research. She conducts systematic reviews that are used to develop clinical practice guidelines and to inform other health decisions. She served on the National Academies Committee on Endocrine-Related Low-Dose Toxicity and Committee on Gulf War and Health: Treatment of Chronic Multisymptom Illness. Dr. Robinson received her MSc in health sciences from the University of Waterloo, Ontario, and her PhD in epidemiology from the Bloomberg School of Public Health.

**Richard P. Scheines** is a professor of philosophy and dean of the Dietrich College of Humanities and Social Sciences of Carnegie Mellon University. His research focuses on causal discovery, specifically the problem of learning about causation from statistical evidence. Dr. Scheines also works in building and researching the effectiveness of educational software, including intelligent proof tutors and virtual causality laboratories, and a full-semester course on causal and statistical reasoning. Because of that work, he has a courtesy appointment in the Human-Computer Interaction Institute of Carnegie Mellon. He served on several National Academies committees, including the Committee to Review the IRIS Process. Dr. Scheines received a PhD in the history and philosophy of science from the University of Pittsburgh.

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**Lauren Zeise** is director of the California Environmental Protection Agency's Office of Environmental Health Hazard Assessment. She oversees the department's activities, which include the development of risk assessments, hazard evaluations, toxicity reviews, cumulative impact analyses, frameworks and methods for assessing toxicity and cumulative effects of vulnerability and environmental exposures on communities, and the department's activities in the California Environmental Contaminant Biomonitoring Program. Dr. Zeise was the 2008 recipient of the Society for Risk Analysis Outstanding Practitioners Award. She has served on advisory boards and committees of the US Environmental Protection Agency, the Office of Technology Assessment, the World Health Organization, and the National Institute of Environmental Health Sciences. Dr. Zeise has served on numerous National Academies committees, including the Committee on Toxicity Testing and Assessment of Environmental Agents and the Committee on Improving Risk Analysis Approaches Used by the U.S. Environmental Protection Agency. Dr. Zeise received a PhD from Harvard University.

**Yiliang Zhu** is a professor in the Division of Epidemiology, Biostatistics, and Preventive Medicine of the University of New Mexico (UNM) School of Medicine. He directs the biostatistics, epidemiology, and research design cores for the UNM Clinical and Translational Research Center and for the Mountain West Clinical and Translational Research Infrastructure Network, a consortium of 13 universities in seven states. His research focuses on quantitative methods in health risk assessment, including integrative modeling of biologic systems, dose-response modeling, benchmark-dose methods, and uncertainty quantification. He also conducts research in biostatistics methods, clinical- and health-outcome evaluation, and impact assessment of health-care systems and policies in northwestern rural China. Before joining UNM, Dr. Zhu was a professor at the University of South Florida College of Public Health where he directed the Biostatistics PhD program and the Center for Collaborative Research. Dr. Zhu has served on several National Academies committees, including the Committee on EPA's Exposure and Human Health Assessment of Dioxin and Related Compounds, the Committee on Tetrachloroethylene, the Committee to Review EPA's Draft IRIS Assessment of Formaldehyde, and the Committee to Review the IRIS Process. He received a PhD in statistics from the University of Toronto.

## **Appendix B**

### **Open Session Workshop Agenda**

#### **COMMITTEE TO REVIEW ADVANCES MADE TO THE IRIS PROCESS**

#### **SECOND MEETING**

Open Session: February 1-2, 2018  
National Academies of Sciences, Lecture Room  
2101 Constitution Ave, NW  
Washington, DC 20418

#### **OPEN SESSION AGENDA**

- 9:30 **Purpose of Open Session and Introduction of Committee Members**  
Jonathan Samet  
*Chair, Committee to Review Advances Made to the IRIS Process*  
*Dean, Colorado School of Public Health*
- 9:45 **Introduction and Overview of Improvements to the IRIS Program**  
Tina Bahadori  
*Director, National Center for Environmental Assessment*  
*U.S. Environmental Protection Agency*
- Kristina Thayer  
*Director, Integrated Risk Information System (IRIS) Division*  
*U.S. Environmental Protection Agency*
- 10:45 **Discussion with National Academies Committee**
- 11:30 **Opportunity for Public Comments to National Academies Committee**
- 12:00 *Lunch Break*
- 1:00 **Session 1: Systematic Review in the IRIS Program – Evidence Identification**  
  
*EPA Panel Presentations and Discussion with the National Academies Committee on the Following Topics:*
- Scoping, Problem Formulation, and Protocols  
Literature Searching, Screening, and Inventories

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2:00 **Opportunity for Public Comments to National Academies Committee**

2:15 **Session 2: Systematic Review in the IRIS Program – Evidence Evaluation**

*EPA Panel Presentations and Discussion with the National Academies Committee on the Following Topics:*

Evaluating Individual Studies: Reporting Quality, Risk of Bias, and Sensitivity

Evaluating Confidence in a Body of Evidence: Evidence Synthesis and Integration to Reach Hazard Conclusions

3:15 **Opportunity for Public Comments to National Academies Committee**

3:30 *Break*

3:45 **Session 3: Development and Application of Specialized Tools for Systematic Review**

*EPA Panel Presentations and Discussion with the National Academies Committee*

4:30 **Opportunity for Public Comments to National Academies Committee**

5:00 *Break*

5:30-  
7:00 **Poster Session and Demonstrations, West Court**

**FRIDAY, FEBRUARY 2, 2018**

8:30 **Welcome and Recap from First Day**

Jonathan Samet

*Chair, Committee to Review Advances Made to the IRIS Process*

*Dean, Colorado School of Public Health*

8:45 **Session 4: Study Selection for Developing Toxicity Values, and Advancing Research on Quantitative Analyses for Evidence Integration and Dose-Response Analyses**

*EPA Panel Presentations and Discussion with the National Academies Committee*

10:00 **Opportunity for Public Comments to National Academies Committee**

10:15 *Break*

10:30 **Collaborations, Training, and Final Thoughts**

Tina Bahadori

*Director, National Center for Environmental Assessment*

*U.S. Environmental Protection Agency*

Kristina Thayer

*Director, Integrated Risk Information System (IRIS) Division*

*U.S. Environmental Protection Agency*

*Appendix B*

11:00 **Discussion with National Academies Committee**

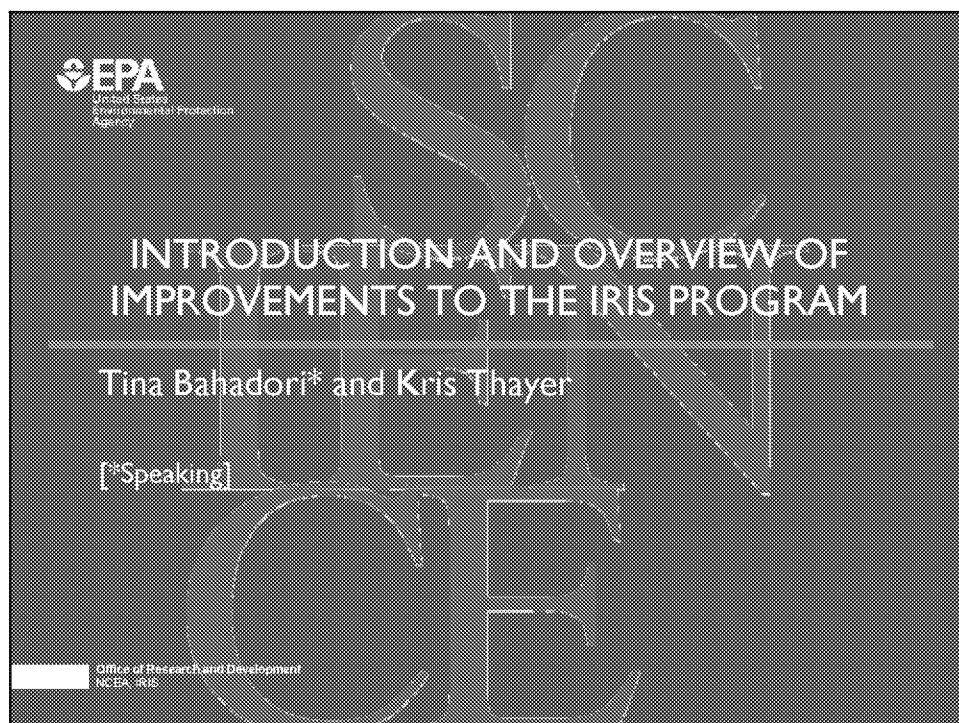
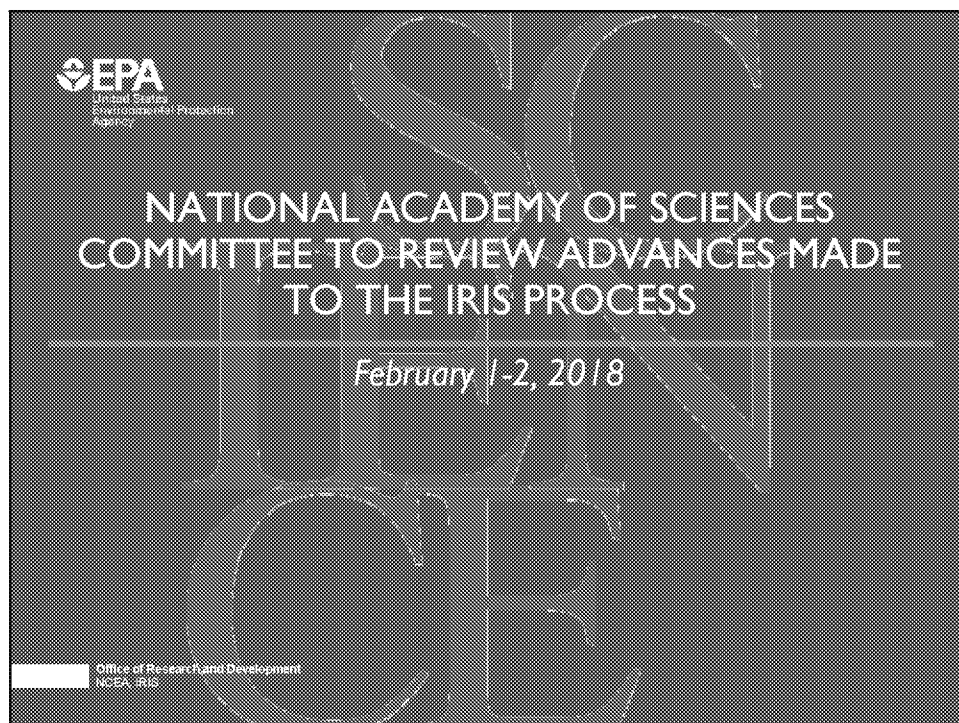
11:45 **Opportunity for Public Comments to National Academies Committee**

12:30 *Adjourn*



## **Appendix C**

### **Presentations by US Environmental Protection Agency**

*Appendix C*




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- **Created in 1985 to foster consistency in the evaluation of chemical toxicity across the Agency.**
- **IRIS assessments contribute to decisions across EPA and other health agencies.**
- **Toxicity values**
  - ... Noncancer: Reference Doses (RfDs) and Reference Concentrations (RfCs).
  - ... Cancer: Oral Slope Factors (OSFs) and Inhalation Unit Risks (IURs).
- **IRIS assessments have no direct regulatory impact until they are combined with**
  - ... Extent of exposure to people, cost of cleanup, available technology, etc.
  - ... Regulatory options.
  - ... Both of these are the purview of EPA's program offices.

2






**IRIS Provides Scientific Foundation for Agency Decision Making**

IRIS

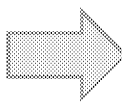
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- **Clean Air Act (CAA)**
- **Safe Drinking Water Act (SDWA)**
- **Food Quality Protection Act (FQPA)**
- **Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA)**
- **Resource Conservation and Recovery Act (RCRA)**
- **Toxic Substances Control Act (TSCA)**


**Broad Input to Support**



- **Agency Strategic Goals**
- **Children's Health**
- **Environmental Justice**

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## Appendix C



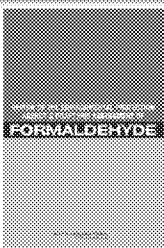
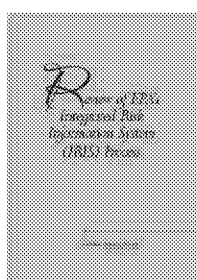

### New Leadership Structure in NCEA

- **In January 2017, EPA appointed new leadership to the National Center for Environmental Assessment and to its IRIS Program.**
  - **NCEA Director:** significant experience in the chemical and energy industries, and formerly the Director of ORD's Chemical Safety for Sustainability National Research Program, Tina Bahadori brings knowledge of TSCA, innovative applications of computational toxicology, and exposure science.
  - **IRIS Program Director:** As a recognized leader in systematic review, automation, and chemical evaluations, Kris Thayer brings experience in early partner and stakeholder engagement and input, and demonstrated actions to increase capacity and transparency in assessments.
- **Improved responsiveness and accountability through Senior Leadership Team.**
- **Integrating across the spectrum of human and ecological RA practices.**

4



### Drivers for this Study






[https://www.gao.gov/highrisk/transforming\\_epa\\_and\\_toxic\\_chemicals/why\\_did\\_study](https://www.gao.gov/highrisk/transforming_epa_and_toxic_chemicals/why_did_study)

**Fiscal Year 2017 Appropriations**  
<https://www.congress.gov/114/crpt/srpt281/CRPT-114srpt281.pdf>

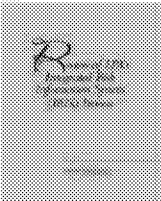
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## NAS (2014) Overarching Statements

2014




"Overall, the committee finds that substantial improvements in the IRIS process have been made, and it is clear that EPA has embraced and is acting on the recommendations in the NRC formaldehyde report. The NRC formaldehyde committee recognized that its suggested changes would take several years and an extensive effort by EPA staff to implement. Substantial progress, however, has been made in a short time..." [p.9]

"EPA has not only responded to the recommendations made in the NRC formaldehyde report but is well on the way to meeting the general systematic-review standards for identifying and assessing evidence." [p. 51]

"... the IRIS program has moved forward steadily in planning for and implementing changes in each element of the assessment process. The committee is confident that there is an institutional commitment to completing the revisions of the process..." [p.135]

"The committee commends EPA for its substantive new approaches, continuing commitment to improving the process, and successes to date. Overall the committee expects that EPA will complete its planned revisions in a timely way and that the revisions will transform the IRIS Program." [p.135]

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## Previous Phased Improvements to the IRIS Program

- **Revising the structure of assessments to enhance the clarity and transparency of presentation:**
  - Detailing the methods underlying each step of draft development (e.g., literature search strategy).
  - Restructuring the document into separate hazard identification and dose-response chapters.
  - Replacing lengthy study summaries with synthesis text, supported by standardized tables and graphs.
- **Implementing "IRIS Enhancements"**
  - An updated process for developing and reviewing assessments that increases public input and peer consultation at earlier stages of assessment development, and clarifies processes for considering new evidence and scientific issues.
- **Establishing the SAB Chemical Assessment Advisory Committee (CAAC)**
  - 5 IRIS assessments completed CAAC review since 2014.
- **Restructuring the IRIS Program to create expertise-specific workgroups and improved assessment oversight.**

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## Appendix C



### Quality Management

- **Assessment Development and Review**
  - Quality management inherent to systematic review methodology (e.g., independent screening of studies)
  - Rigorous review process includes internal, public, and external peer review
- **Scientific Support Teams**
  - Systematic review methods (Systematic Review Workgroup)
  - Systematic review support to chemical assessment teams (e.g., screening, study evaluation, data extraction, use of specialized software, etc. – train the trainer model)
  - Discipline-specific workgroups (e.g., epidemiology, PBPK, neurotoxicology, etc.)
  - Executive oversight
- **Roles and Responsibilities**
  - Assessment plans, protocols, and draft assessments indicate contributors and roles
  - Given current budget there is very limited use of contract support to conduct assessments
- **Training**
  - regular training via skill-building seminars, focused discussions, and retreats

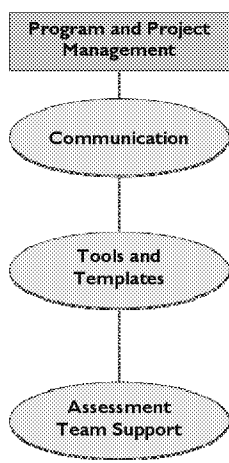
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### Improved Practices for Timeliness and Resource Management

**Current Program and Project Management in IRIS:**

- *Centralized communication processes* for providing staff with updates on near-term priorities, template materials, and other process-oriented decisions.
- *Development and maintenance* of templates and checklists for key steps of assessment development using Microsoft SharePoint and Project as collaborative, web-based tools for assessment teams and project managers (document management and storage; scheduling support).
- *Dedicated IRIS Program staff and on-site programmatic contractor support* to facilitate continued implementation of program and project management principles.




```

graph TD
    A[Program and Project Management] --> B([Communication])
    B --> C([Tools and Templates])
    C --> D([Assessment Team Support])
            
```

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## GAO 2017 Report

- **Acknowledged the actions ORD has taken to enable the IRIS Program to produce timely, transparent, and credible assessments in support of EPA's mission.**
- **Discussions with GAO during and after the release of the 2017 High Risk Report have focused on approaches to demonstrate how management and integrity initiatives within IRIS are supporting the transformation of the program**

GAO High Risk Criteria	2015 Rating	2017 Rating
Leadership Commitment	Met	Met
Monitoring	Partially Met	Met
Action Plan	Partially Met	Partially Met
Demonstrated Progress	Not Met	Partially Met
Capacity	Not Met	Partially Met

- **IRIS is engaged in continual ongoing discussion with GAO regarding recommendations from the 2008, 2012, and 2013 reports.**
- **Of the seventeen recommendations issued in these three reports, as of June 2017, we have successfully closed ten recommendations and are rapidly moving to address the remaining seven.**

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## IRIS Multi-Year Agenda

- **Released to the public December 2015**
  - Result of a survey EPA program and regional offices for their assessment needs balanced with resource availability.
  - Other chemicals were also carried over from earlier prioritizations
  - Reflects global priorities
- **In FY 2018, reaffirm priorities; identify new or more urgent needs.**
- **Engage states.**

Group	Chemicals
1	Manganese
	Mercury/methylmercury
	Nitrate/nitrite
	Perfluoroalkyl compounds
	Vanadium and compounds
2	Acetaldehyde
	Ammonia (oral)
	Cadmium and compounds
	Uranium
3	Di-(2-ethylhexyl) phthalate
	Dichlorobenzene isomers
	Methyl t-butyl ether (MTBE)
	Nickel and compounds
	Styrene

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## Appendix C



### A Portfolio Approach

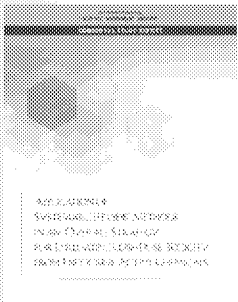
- **Moving away from a ‘one-size-fits-all’ approach to risk assessment towards a spectrum of assessment products to meet specific decision contexts;**
- **Facilitating the incorporation of new science into risk assessment and decision-making;**
- **Enabling assessments to be better tailored to meet needs of decision makers;**
- **Increasing the number of chemicals that can be evaluated for their effects on human health by utilizing constrained resources in the most efficient manner.**

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### Leading Edge of Science – Systematic Review

**NAS 2017:  
Reflections and  
Lessons  
Learned from  
the Systematic  
Review**



“...one disadvantage in conducting a systematic review is that it can be time and resource intensive, particularly for individuals that have not previously conducted a systematic review.” [p.157]


“The committee discussed at length whether it could provide EPA with advice about when a systematic review should be performed but decided it could not be more specific because that decision will depend on the availability of data and resources, the anticipated actions, the time frame for decision making, and other factors.” [p.157]

“...committee also recognized that it might be advantageous for EPA to build on existing systematic reviews that are published in the peer-reviewed literature.” [p.157]

“...committee recognizes that the methods and role of systematic review and meta-analysis in toxicology are evolving rapidly and EPA will need to stay abreast of these developments, strive for transparency, and use appropriate methods to address its questions.” [p.157]

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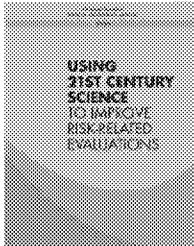
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## Leading Edge of Science – New Data Streams

### Next Generation IRIS

- **IRIS in the 21st Century** – implement recommendations of the NAS 2017 report, *Using 21st Century Science to Improve Risk-Related Evaluations*;
- **New Approach Methods** – see poster session
- **Collaborate with Tox21**
  - ... build expert-judgment case studies that inform assessment development and fill gaps in assessments, especially for data poor chemicals;
  - ... inform where resources should be strategically invested to generate additional data.
- **Create efficiencies** – engage other agencies to share common practices, data, and tools, and more efficiently leverage resources across the federal government.
- **Refresh science** – MOU's with academia and other federal agencies; strategic staffing; deeper engagement with health agencies in states.



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## How is IRIS Evolving?


- **Increase transparency and full implementation of systematic review**
  - ... implement using approaches that foster consistency across the IRIS Program; many active and all new starts address systematic review-related recommendations of 2014 NAS report
- **Modernize the IRIS Program**
  - ... through automation and machine learning to expedite systematic review, incorporation of emerging data types
- **Modularize product lines**
  - ... implement a portfolio of chemical evaluation products that optimize the application of the best available science and technology. These products will allow IRIS to remain flexible and responsive to clients within the EPA as well the diverse collection of stakeholders beyond EPA, including states, tribal nations, and other federal agencies.
- **Enhance accessibility**
  - ... provide outreach and training to make systematic review practices ubiquitous and more accessible; enhance data sharing through publicly available software platforms for assessments developed by EPA, other federal and state agencies, industry, academia and other third-parties.

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Appendix C

<div>  <div>IRIS has Addressed the Major NAS 2014 Recommendations</div> </div>	
NAS 2014 Topics	IRIS Process Improvements
General Process Issues (Chapter 2)	<ul style="list-style-type: none"> <li>• Quality management pipeline implemented</li> <li>• Program and project management processes implemented</li> <li>• Frequent opportunities for stakeholder engagement</li> </ul>
Future Directions (Chapter 8 “Lessons Learned” and “Looking Forward”)	<ul style="list-style-type: none"> <li>• Processes being implemented include flexibility to incorporate evolving methods in systematic review and risk assessment</li> <li>• Increased collaboration with federal partners and international experts prevents duplication of effort and maintains cutting edge approaches</li> <li>• Current research efforts and training serve to ensure that methods and staff are able to adapt to changing scientific contexts and sources of evidence, including new and emerging data types</li> </ul>

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## SESSION I: SYSTEMATIC REVIEW IN THE IRIS PROGRAM - EVIDENCE IDENTIFICATION

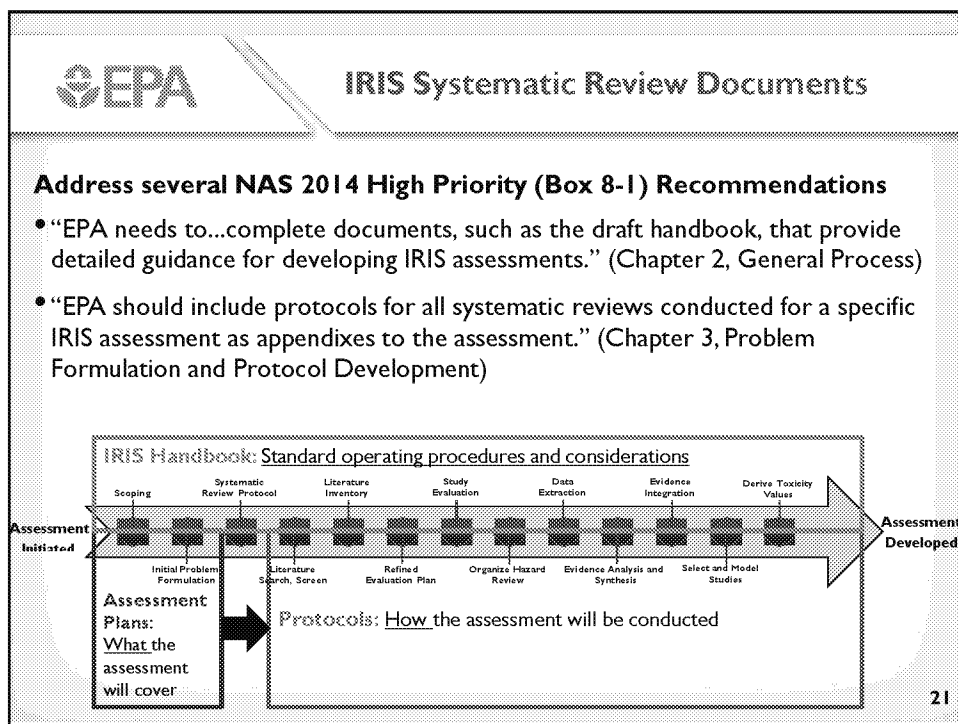
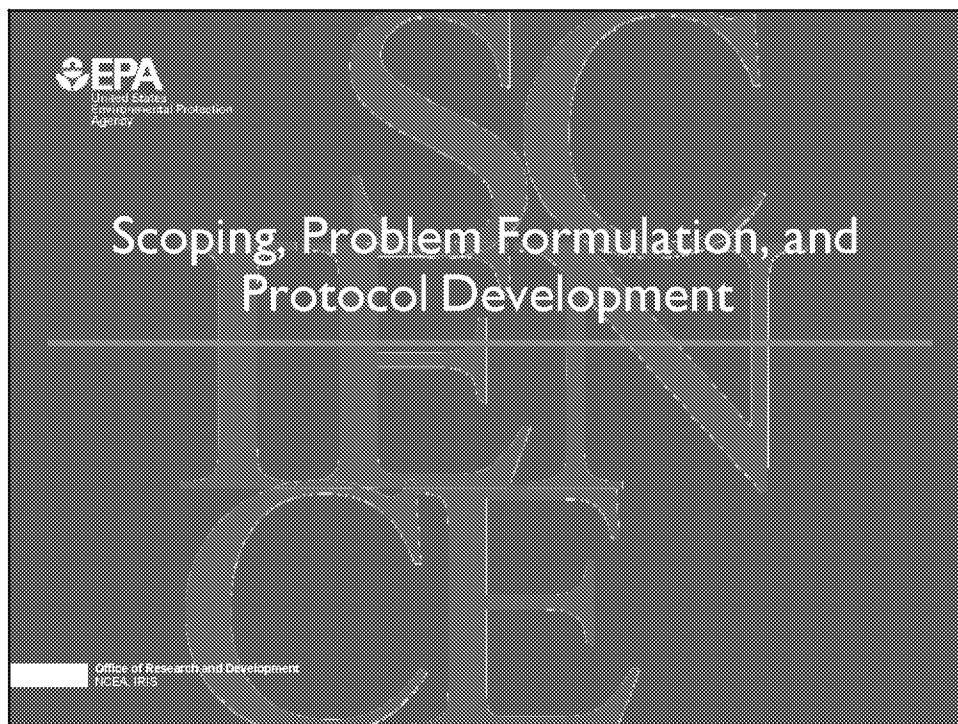
Kris Thayer\*, Andrew Kraft\*, April Luke, Beth Radke, Michele Taylor

[\*Speaking]


Office of Research and Development  
NOEA, IRIS



## Appendix C

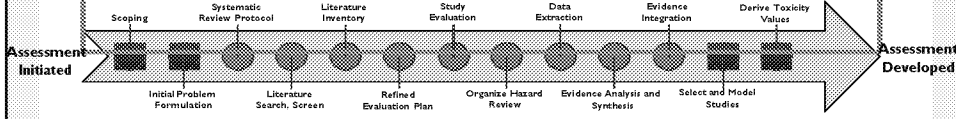


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## IRIS Handbook

**IRIS Handbook: Approaches and considerations for applying principles of systematic review to IRIS assessments, general frameworks, and examples.**

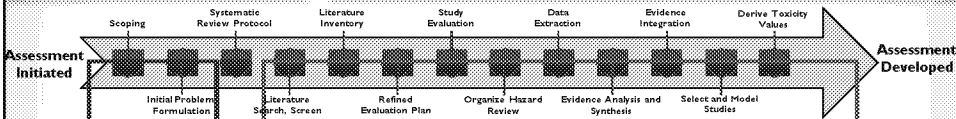


- IRIS Handbook level of detail aimed for EPA staff and contractors, e.g., use of HERO, timelines for internal review steps, etc.
- Currently being updated to reflect Agency input, evolving IRIS practices as systematic review approaches are tested through implementation, and public comment received on chemical-specific protocols (e.g., chloroform)
- Evergreen to reflect future advances
- Anticipate public release in 2018

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## IRIS Assessment Plans and Protocols



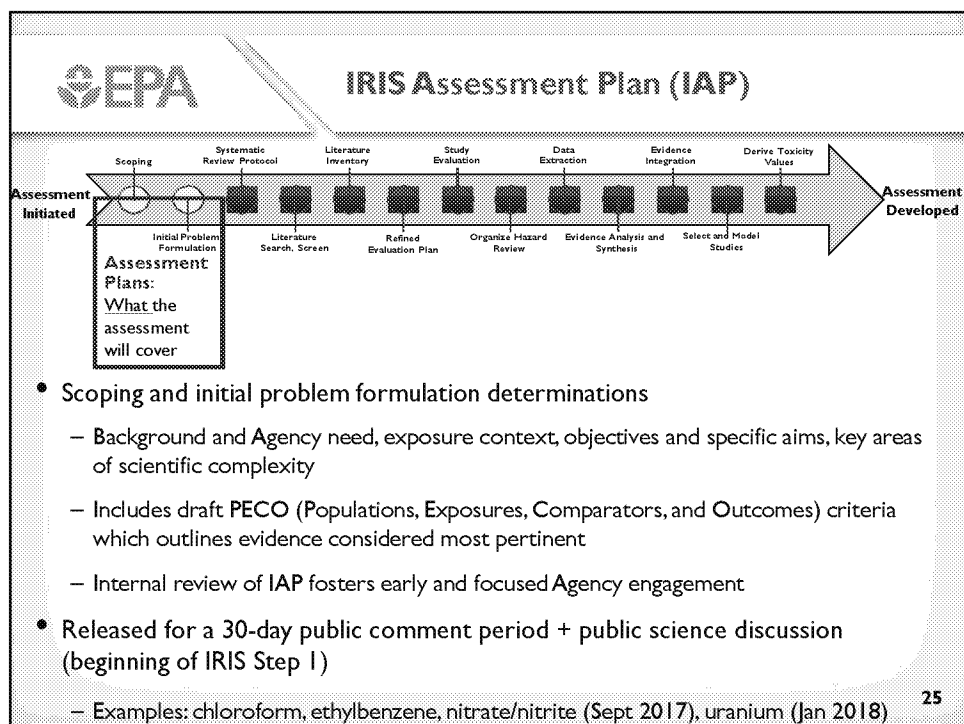
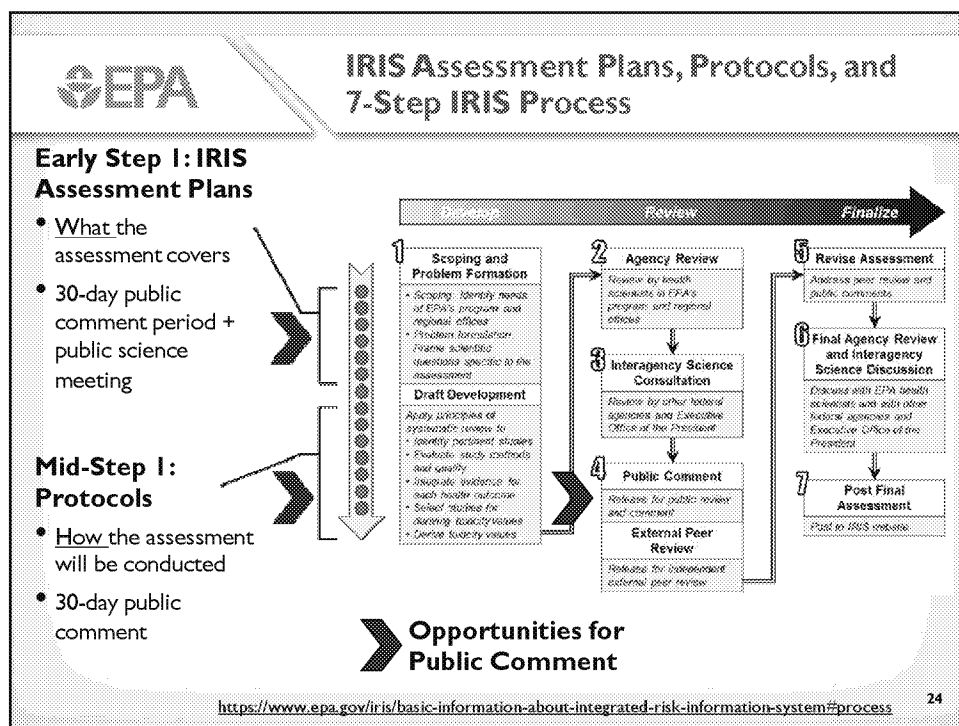
**Assessment Plans:** What the assessment will cover

**Protocols:** How the assessment will be conducted (specific procedures and approaches for each assessment component, with rationale where needed)

- Chemical-specific documents
- IRIS Assessment Plans (IAPs) are problem formulation and scoping documents that include more elements of systematic review
- Protocols outline methods, including updates to the IAPs
- IAPs and protocols include proposed “modularity,” targeted focus and use of existing assessments
- Templates created to promote consistency across the IRIS Program, which is implemented across NCEA divisions and geographical locations

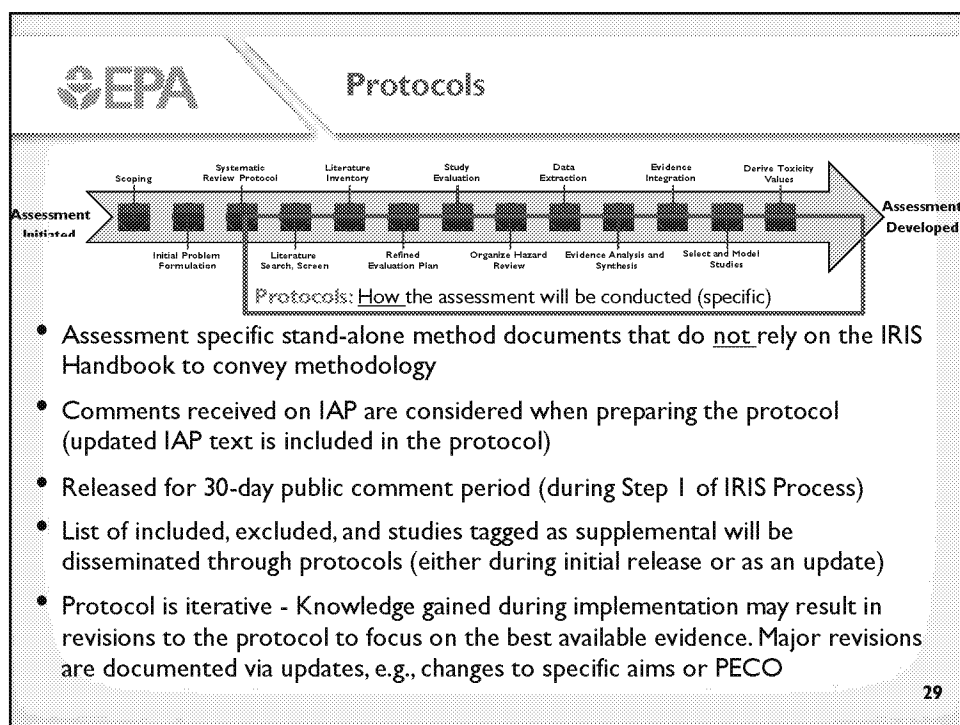
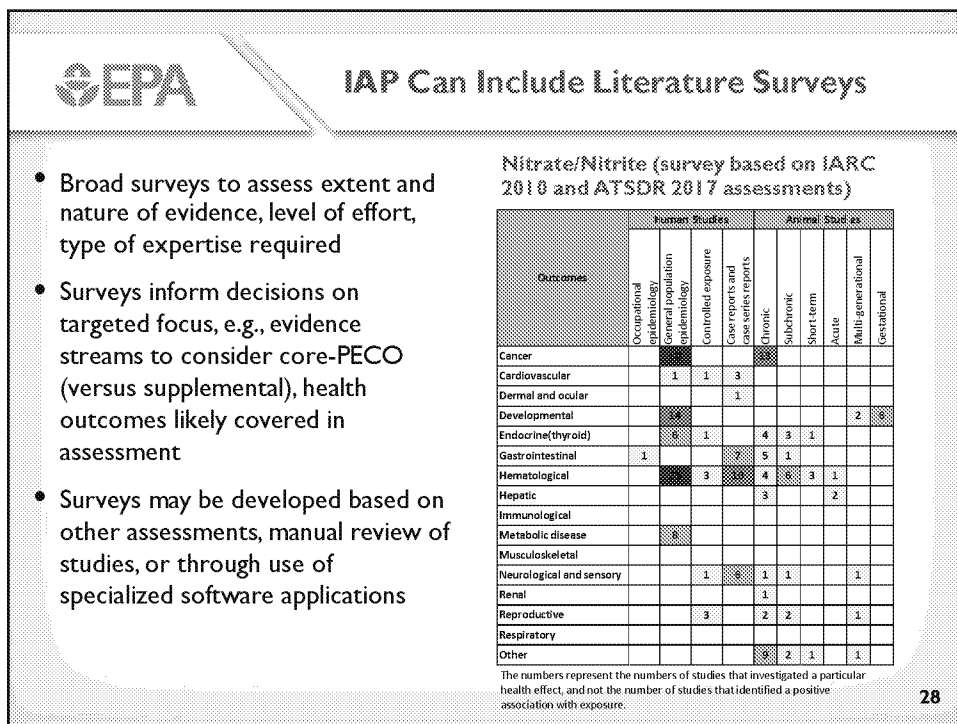
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## Appendix C






## Appendix C






## Appendix C



### Publicly Available Examples

<p><b>Assessment Plans</b></p> <p>September 27-28, 2017</p> <ul style="list-style-type: none"> <li>• Chloroform</li> <li>• Nitrate/nitrites</li> <li>• Ethylbenzene</li> </ul> <p>January 26, 2018</p> <ul style="list-style-type: none"> <li>• Uranium</li> </ul> <p><b>Protocol</b></p> <p>January 26, 2018</p> <ul style="list-style-type: none"> <li>• Chloroform (includes list of included studies)</li> </ul> <p><b>Rapid systematic review</b></p> <ul style="list-style-type: none"> <li>• EPA response to the Chloroprene Request for Correction (posted January 29, 2018)</li> </ul>	<ul style="list-style-type: none"> <li>• <b>Targeted focus:</b> chloroform, uranium, chloroprene</li> <li>• <b>Modularity:</b> ethylbenzene</li> <li>• <b>Use of existing assessments conducted by others:</b> nitrate/nitrate, uranium (ATSDR assessments)</li> <li>• IAPs and/or protocols will be released for most in-progress assessments                             <ul style="list-style-type: none"> <li>• Which document is released depends on extent of refinement in scope compared to previous public sharing and maturity of the draft assessment</li> </ul> </li> </ul>
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# IRIS

## Literature Searching, Screening, and Inventories\*

Office of Research and Development  
NCEA, IRIS

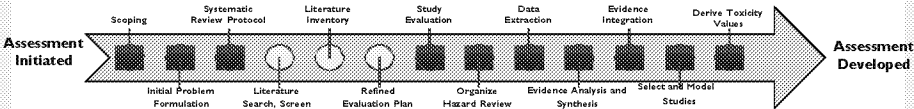
\* includes basic methodological details

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## NAS 2014: High Priority (Box 8-1) Recommendations


“...include a section on evidence identification that is written in collaboration with information specialists trained in systematic reviews and that includes a search strategy for each systematic-review question being addressed in the assessment. Specifically, the protocols should provide a line-by-line **description of the search strategy, the date of the search, publication dates searched, and explicitly state the inclusion and exclusion criteria...**”



The flowchart shows the progression from 'Assessment Initiated' to 'Assessment Developed'. It includes steps: Scoping, Systematic Review Protocol, Literature Inventory, Study Evaluation, Data Extraction, Evidence Integration, and Derive Toxicity Values. Below these are sub-steps: Initial Problem Formulation, Literature Search, Screen, Refined Evaluation Plan, Organize Hazard Review, Evidence Analysis and Synthesis, and Select and Model Studies.

- Protocols outline the specifics of the literature search and screening approaches, including inclusion and exclusion criteria in PECO tables
- Dedicated information technologists help formulate searches, and screening decisions are tracked in HERO (tagging)
- Manual and semi-automated approaches are being used to identify relevant studies
- Inventories of basic study methods organize evidence for refinement and evaluation
- Changes and updates are documented in the protocol

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## Routine Evidence Identification Processes

### Database Searches

- Identify peer-reviewed and “gray” (unpublished) literature
- PubMed, ToxLine, and Web of Science are standard (others can be included as needed)
- Conduct regular search updates
- Details of search strategy, dates, and retrieved records are presented in protocols and assessments

### Screening

1. Title/abstract
2. Full text

- Use manual and automated approaches
- ≥ 2 screeners
- Tag studies as excluded, meeting PECO criteria, or supplemental information
- Screening decisions available in HERO
- Typically do not apply language-restrictions
- Review reference list of included studies and relevant reviews to identify studies missed from database searches
- Share list of included studies with public to further ensure all relevant studies included

### Inventories

#### Health Outcome & PBPK Studies

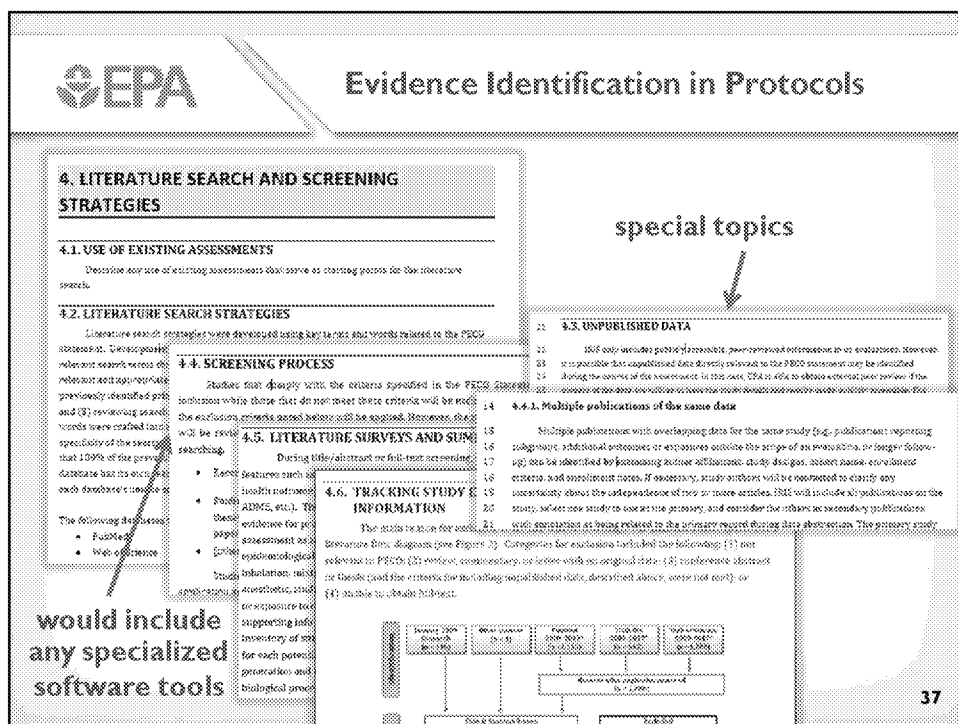
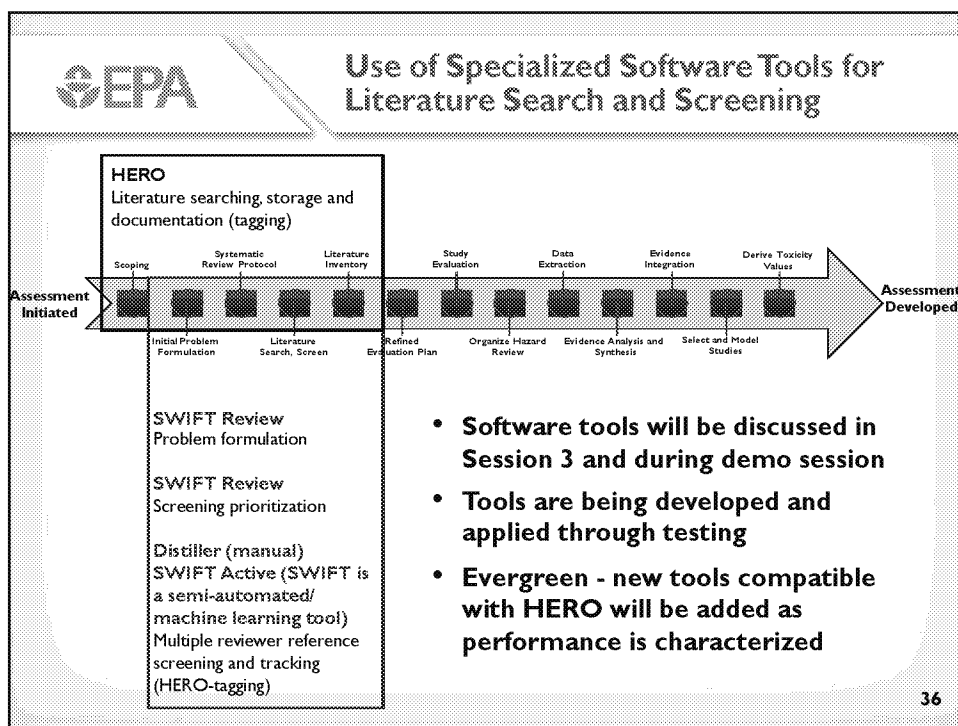
- Tag studies by line of evidence and outcome
- Distribute to disciplinary experts for review

#### Supplemental Studies

- Includes in vitro and other mechanistic evidence (e.g., non-PECO exposure route; non-PECO animal model; toxicokinetic data)
- Inventories contain basic study methods for evaluation and prioritization decisions

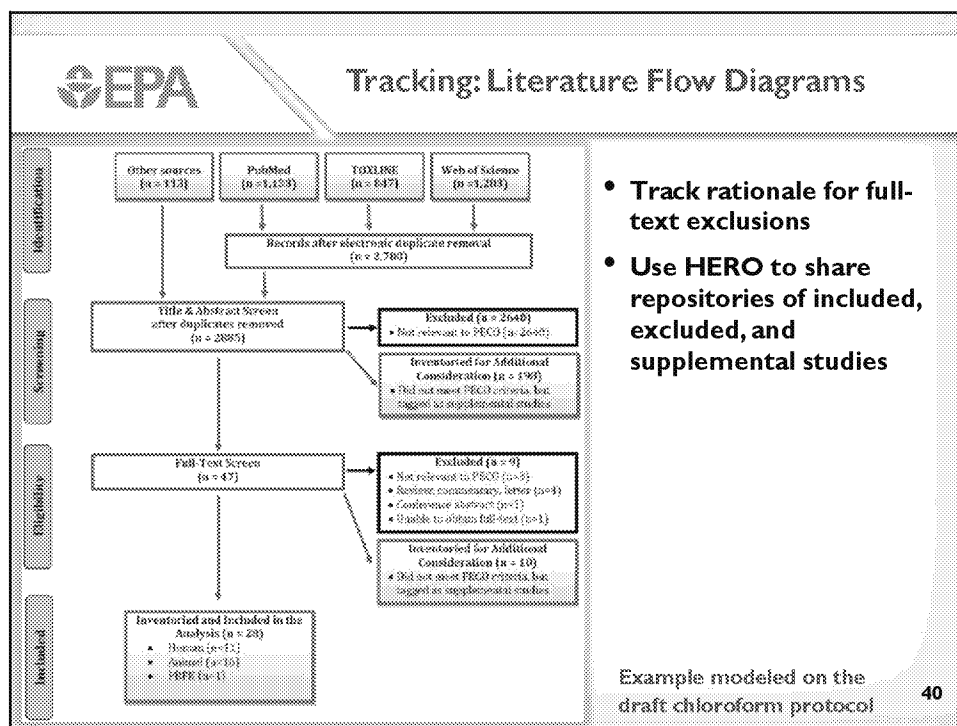
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## Appendix C





## Appendix C



**EPA** **Literature Inventories**

**Example Details Routinely Extracted** (*female reproductive toxicity in animals*):

- Outcome category (e.g., fertility) and/or Specific endpoint (e.g., number of litters)
- Species (e.g., rat; alternative [nonmammalian] animal)
- Exposure duration (e.g., chronic; multi-generational; gestational)
- Exposure route (e.g., oral [gavage]; in vitro)

**Assessment-Specific Extraction Details** (*generic examples*):

- Exposure levels tested
- Test article details, such as purity or isomeric composition


**Results are Typically Not Included in Inventories**

**Developing Extraction Forms** (*all 3 lines of evidence*) to be interoperable with HAWC

Test compound	DSP	Material age at int. gestational exp.	NA
Species	Rat	Subject age at in vivo exposure initiation	Px021
Exposure type	In vivo	Lifespan at in vivo exposure initiation	Meaning
In vivo exposure route	Oral gavage	Dose/concentration	0.500 mg/kg d5y
Strain of exposed test model	Sprague-Dawley	Exposure duration	Single exposure
Sex of exposed test model	M	Exposure period	Postnatal only

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## Refined Evaluation Plan (optional)

**Discipline-specific experts consider whether and how to further refine or prioritize studies/outcomes for evaluation (based on study design features)**

- *Health effect studies meeting PECO criteria (e.g., organized by outcome):*
  - Considers ADME and other key science issues (supplemental studies reviewed)
  - Opportunity to discuss outcome grouping (e.g., based on known biology/MOA) and handling of key science issues during outcome-specific study evaluations
  - Studies with certain design features or specific outcomes may be selected or prioritized for evaluation and synthesis (e.g., based on exposure duration, administration, or levels tested; or endpoint specificity)
- *Supplemental mechanistic studies (e.g., organized by test system, mechanistic event, or key characteristic [of carcinogens]) are considered iteratively:*
  - Identifies other studies on specific aim mechanistic questions (e.g., mutagenicity)
  - Organizes the available evidence to allow for pragmatic evaluations of key issues that arise during review of PECO-specific human and animal studies (Session 2)

**Refinements are tracked and updated in the assessment protocol** 42



## IRIS has Addressed the Major NAS 2014 Recommendations

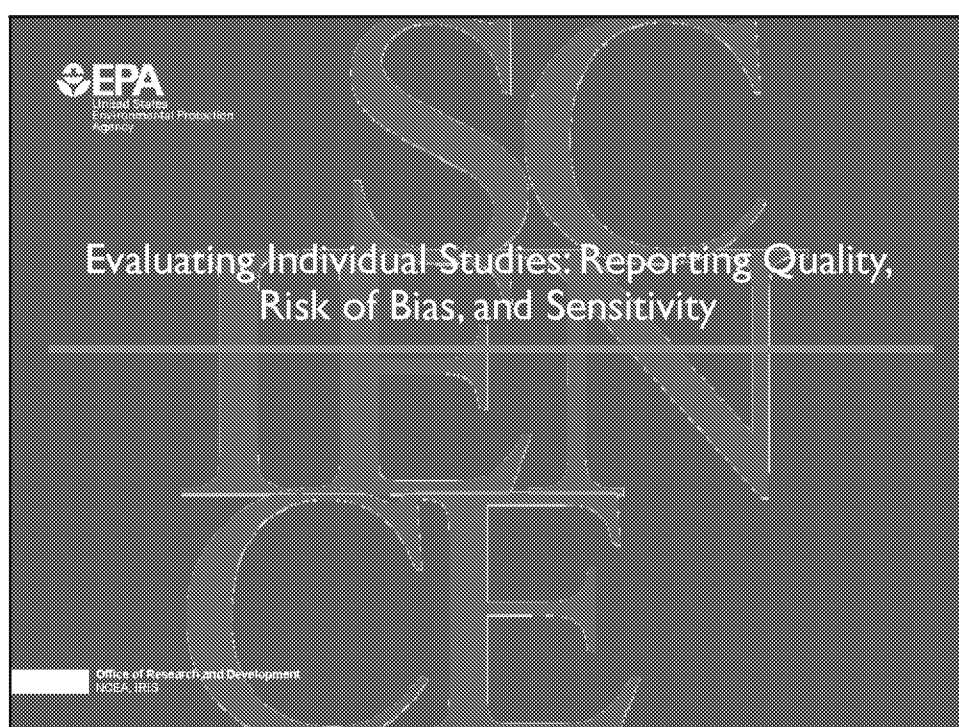
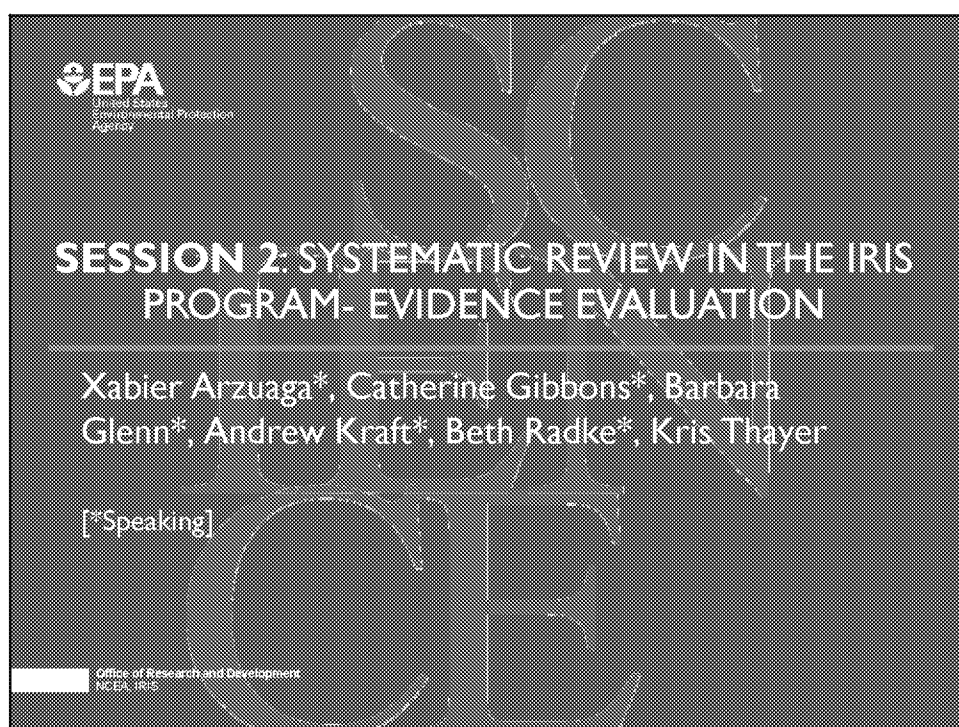
NAS 2014 Topics	IRIS Process Improvements
General Process Issues (Chapter 2); Problem Formulation and Protocol Development (Chapter 3)	<ul style="list-style-type: none"> <li>Draft IRIS Handbook of program SOPs is being reviewed within EPA</li> <li>IAPs allow early comment on problem formulation</li> <li>More frequent Agency engagement facilitates scope refinement</li> <li>Assessment protocols describe methods and allow for iteration</li> <li>Re-occurring staff training and template IAPs and protocols promote consistency and quality control</li> </ul>
Evidence Identification (Chapter 4)	<ul style="list-style-type: none"> <li>Consultation with information technologists and subject experts</li> <li>Adopts current systematic review best practices, including use of specialized tools</li> <li>Transparent documentation (e.g., literature flow diagrams)</li> </ul>

**See Demonstrations:**


- Sciome Workbench for Interactive computer-Facilitated Text mining (SWIFT Review and SWIFT Active)
- Health Assessment Workspace Collaborative (HAWC)
- Heath Effects Research Online (HERO)

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*Appendix C*



*Progress Toward Transforming the Integrated Risk Information System Program: A 2018 Evaluation*




**NAS 2014 High Priority (Box 8-1)**  
**Recommendations on Evidence Evaluation**

“When considering any method for evaluating individual studies, EPA should **select a method that is transparent, reproducible, and scientifically defensible**. Whenever possible, there should be empirical evidence that the methodologic characteristics that are being assessed in the IRIS protocol have systematic effects on the direction or magnitude of the outcome.”

“EPA should **specify the empirically based criteria it will use to assess risk of bias for each type of study design in each type of data stream**.”

“To maintain transparency, EPA should **publish its risk-of-bias assessments as part of its IRIS assessments**.”

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**Study Evaluation –  
Developing an Approach**

- Considered and drew from existing tools for study evaluation.
- Developed approaches for both epidemiology and toxicity studies that:
  - Addresses study sensitivity and identifies potential sources of bias.
  - Transparently presents the criteria/considerations used to consistently evaluate and judge each study/outcome.
  - Provides access to the rationale for discipline-specific decisions made during the evaluation process.
- Objective of the approach: Identify the most informative and reliable studies for evidence synthesis and integration.

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# Appendix C

EPA PBPK Model Evaluation		Prior to use, relevant PBPK models will:
Criteria	Example information	
Scientific	Biological basis for the model is accurate <ul style="list-style-type: none"> <li>e.g., Predicts dose metrics expected to be relevant</li> </ul>	<ul style="list-style-type: none"> <li>Be thoroughly evaluated based on scientific and technical criteria (examples to the left).</li> <li>Undergo QA/QC on model equations, parameters (including primary/secondary sources), and model code.</li> </ul>
	Consideration of model fidelity to the biological system strengthens the scientific basis relative to standard extrapolation (default) approaches <ul style="list-style-type: none"> <li>e.g., Can the model describe critical behavior, such as nonlinear kinetics in a relevant dose range, better than the default (i.e., BW<sup>3/4</sup> scaling)?</li> </ul>	
	Principle of parsimony (i.e., model complexity or biological scale should be commensurate with data available to identify parameters)	
	Model describes existing PK data reasonably well, both in "shape" (e.g., matches curvature) and quantitatively (e.g., within a factor of 2–3)	
	Model equations are consistent with biochemical and biological understanding	
Initial technical	Well-documented model code is readily available to EPA and public	<b>For details, please see:</b> <ul style="list-style-type: none"> <li>Poster:                             <ul style="list-style-type: none"> <li>Systematic evaluations of PBPK models for human health risk assessment</li> </ul> </li> <li>EPA website:                             <ul style="list-style-type: none"> <li>EPA Response to the Request for Correction of the IRIS Toxicological Review of Chloroprene (2018)</li> </ul> </li> </ul>
	Set of published parameters clearly identified, including origin/derivation	
	Parameters do not vary unpredictably with dose <ul style="list-style-type: none"> <li>e.g., Any dose dependence in absorption constants is predictable across the dose ranges relevant for animal and human modeling</li> </ul>	
	Sensitivity and uncertainty analysis has been conducted for relevant exposure levels (local sensitivity analysis is sufficient, though global preferred) <ul style="list-style-type: none"> <li>e.g., A sound explanation should be provided when sensitivity of the dose metric to model parameters differs from what is reasonably expected</li> </ul>	

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## Evolving Approaches

NTP-ORoC

NTP-OHAT

EPA-IRIS

SciRAP

NavGuide

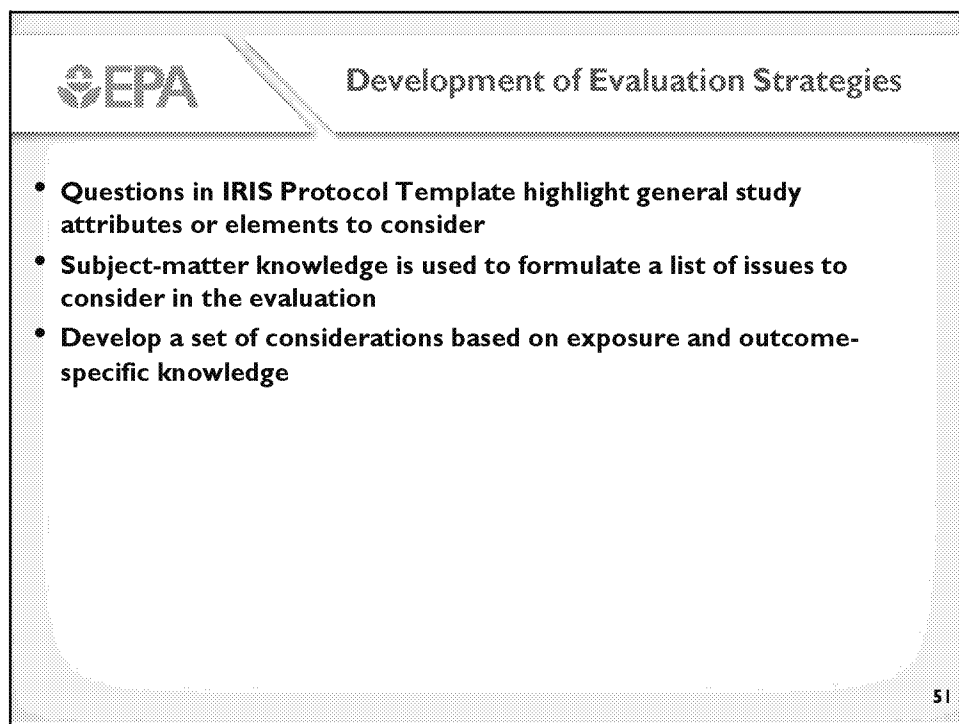
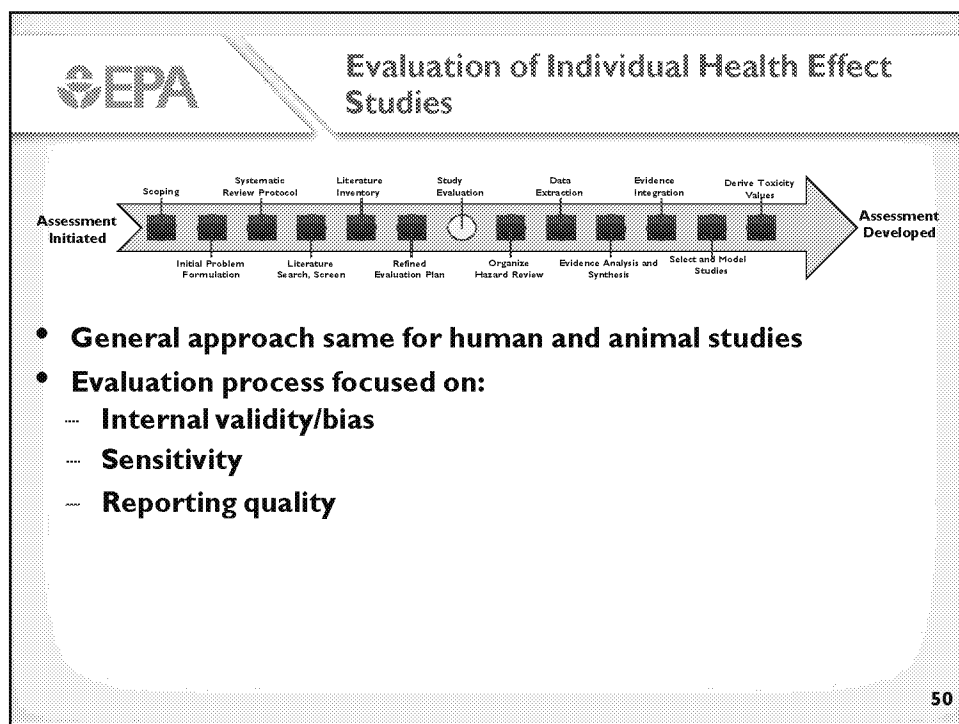
ROBINS-I

ToxRTTool

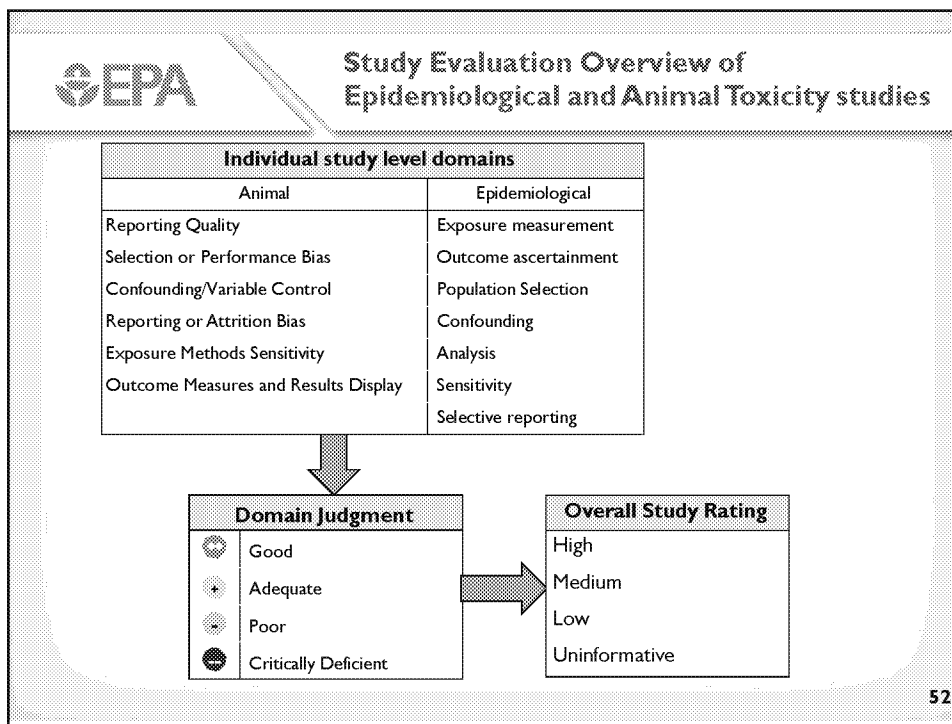
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## Appendix C




**EPA** **Individual Domain Ratings for Epidemiological and Animal Toxicity Studies**


	IRIS Judgment	How to interpret
	Good	Appropriate study conduct relating to the domain & minor deficiencies not expected to influence results.
	Adequate	A study that may have some limitations, but not likely to be severe or to have a notable impact on results.
	Poor	Identified biases or deficiencies interpreted as likely to have had a notable impact on the results or prevent reliable interpretation of study findings.
	Critically Deficient	A judgment that the study conduct relating to the domain introduced a serious flaw that is interpreted to be the primary driver of any observed effect or makes the study uninterpretable. Study is not used without exceptional justification.

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 <b>Overall Study Confidence Ratings for Epidemiological and Animal Toxicity Studies</b>	
Rating	Description
High	No notable deficiencies or concerns identified; potential for bias unlikely or minimal and sensitive methodology.
Medium	Possible deficiencies or concerns noted, but resulting bias or lack of sensitivity would be unlikely to be of a notable degree.
Low	Deficiencies or concerns were noted, and the potential for substantive bias or inadequate sensitivity could have a significant impact on the study results or their interpretation.
Uninformative	Serious flaw(s) makes study results unusable

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 <b>General Considerations to Evaluate Outcomes from Animal Toxicology Studies</b>	
Domain	Metric
Reporting Quality	Reporting of information necessary for study evaluation
Selection or Performance Bias	Allocation of animals to experimental groups
	Blinding of investigators, particularly during outcome assessment
Confounding/Variable Control	Control for variables across experimental groups
Reporting or Attrition Bias	Lack of selective data reporting and unaccounted for loss of animals
Exposure Methods Sensitivity	Characterization of the exposure to the compound of interest
	Utility of the exposure design for the endpoint of interest
Outcome Measures and Results Display	Sensitivity and specificity of the endpoint evaluations
	Usability and transparency of the presented data

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## Appendix C




### Epidemiology Study Evaluation

- **Approach based on the Cochrane Risk of Bias in Nonrandomized Studies of Interventions (ROBINS-I)<sup>1</sup>, modified for environmental and occupational exposures**
- **Start by considering an “ideal” study for each domain, identifying “critical deficiencies”, then developing criteria to define other levels of confidence**
- **Emphasis is on discerning bias that would produce a substantive change in the estimated effect estimate.**

<sup>1</sup>Sterne, Hernan, et al. ROBINS-I: a tool for assessing risk of bias in non-randomized studies of interventions. *BMJ* 2016; 355:i4919.

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### Epidemiology Evaluation Domains

Domain	Core Question
<b>Exposure measurement</b>	Does the exposure measure reliably distinguish between levels of exposure in an appropriate time window?
<b>Outcome ascertainment</b>	Does the outcome measure reliably distinguish the presence or absence (or degree of severity) of the outcome?
<b>Population selection</b>	Is there evidence that selection into or out of the study (or analysis sample) was jointly related to exposure and outcome?
<b>Confounding</b>	Is confounding of the effect of the exposure likely?
<b>Analysis</b>	Does the analysis strategy and presentation convey the necessary familiarity with the data and assumptions?
<b>Sensitivity</b>	Are there concerns for study sensitivity?

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## Example of Considerations by Domains

Domain	Core Question
<b>Exposure measurement</b>	<b>Does the exposure measure reliably distinguish between levels of exposure in an appropriate time window?</b>


**Examples of Prompting Questions:**

- Does the exposure measure capture the variability in exposure among the participants, considering intensity, frequency, and duration of exposure?
- Does the exposure measure reflect a relevant time window?
- Was exposure measurement likely to be affected by knowledge of outcome or by presence of the outcome (i.e., reverse causality)?

**Examples of Follow-up Questions:**

- Is the degree of exposure misclassification likely to vary by exposure level?
- If there is a concern about the potential for bias, what is the predicted direction of the bias on the effect estimate?

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## Study Evaluation: Final Review in HAWC

**Navigation**

- Study Overview
- Study Design
- Study Population
- Study Interventions
- Study Outcomes
- Study Analysis
- Study Reporting
- Study Evaluation

**Final Review edit**

Study Overview

**Study Design**

**Study Population**

**Study Interventions**

**Study Outcomes**

**Study Analysis**

**Study Reporting**

**Study Evaluation**

**Study Overview**

**Study Design**

**Study Population**

**Study Interventions**

**Study Outcomes**

**Study Analysis**

**Study Reporting**

**Study Evaluation**

Questions, instruction text, and drop down rating options are customizable by user

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## Appendix C

### Study Evaluation: Final Review in HAWC

**Elizabeth Radtke**

**Adequate**

Good. Case-control study. 181 cases (71% participation). 50% participation in controls.

Controls identified from previous study of NHL, general pop identified with RDD and Medicare files.

Case participation not assoc. with site, age, or gender. Control participation associated with age, not site or gender.

Copy Notes

Adequate

**Amanda Persad**

**Adequate**

Good-Fair. Cases from SEER. Inclusion criteria and participation rates included. Controls selected either through random digit dialing or Medicare/Medicaid Service files. Eligibility criteria for cases and controls mentioned. Study design is not a cohort or nested case-control design.

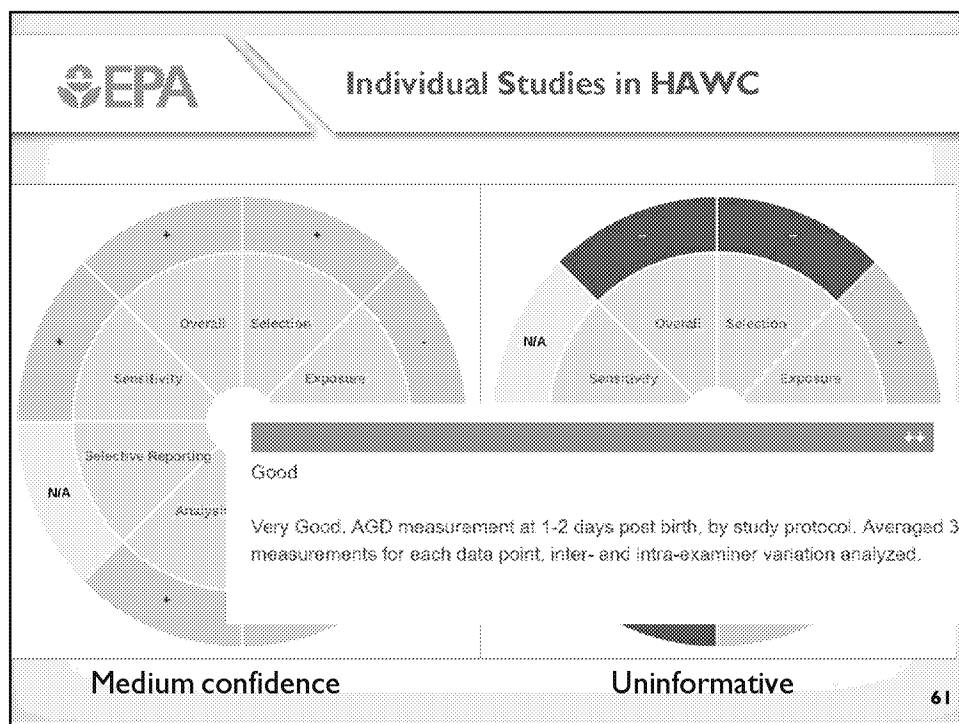
Copy Notes

Normal : B I U

Good-Fair. Case-control study. Cases from SEER. 181 cases (71% participation). 52% participation in controls. Inclusion criteria and participation rates included. Controls selected either through random digit dialing or Medicare/Medicaid Service files. Eligibility criteria for cases and controls mentioned. Study design is not a cohort or nested case-control design. Control participation associated with age.

Questions, drop down, customize

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*Progress Toward Transforming the Integrated Risk Information System Program: A 2018 Evaluation*

## Study Evaluation Summary in HAWC

	Study 1	Study 2	Study 3	Study 4	Study 5	Study 6
Population selection	++	+	++	-	++	+
Exposure measurement	-	-	-	-	-	-
Outcome ascertainment	++	++	++	+	-	++
Confounding	+	+	+	-	+	+
Analysis	++	++	++	+	-	+
Sensitivity	+	-	+	-	-	+
Overall study confidence	M	L	M	L	L	M

Domain judgement		Overall study rating	
++	Good	H	High confidence
+	Adequate	M	Medium confidence
NR	Not reported		
-	Poor	L	Low confidence
-	Critically deficient	U	Uninformative
N/A	Not applicable		

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The logo of the United States Environmental Protection Agency (EPA), featuring a stylized flower/leaf design to the left of the letters "EPA".

## Publicly available examples

- **Initial and iterative improvements to study evaluation**
  - **Ammonia, Inhalation (final 2016)**
  - **RDX (peer review draft 2016)**
  - **TBA (peer review draft 2017)**
  - **ETBE (peer review draft 2017)**
- **Current methods for study evaluation**
  - **Chloroform protocol (2018)**
  - **EPA Response to Chloroprene Request for Correction (2018)**

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